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THE MANAGEMENT OF STAPHYLOCOCCAL DISEASE IN INFANTS AND CHILDREN

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THE increasing incidence and severity of staphylococcal disease are phenomena of grave worldwide concern. Extensive programs aimed toward prevention and eradication of this disease are under development in many countries at the present time.[1-3] Until the aims of prevention and eradication can be realized, however, it is of value to review principles of management applicable to the patient presenting with infection due to *Staphylococcus aureus*.

During the past decade continuous changes in the treatment of staphylococcal disease have been necessary because of differences in the predominant clinical patterns of the disease and the awesome adaptability of the organism. Changing clinical patterns of staphylococcal disease have been noted in all age groups.[4] In the last few years medical literature has contained increasing numbers of epidemics of staphylococcal breast abscess, gastroenteritis, septicemia, and empyema of the newborn infant,[5-8] all entities which were rare prior to 1950. The emergence of "antibiotic resistant" strains following extensive antibiotic usage is a matter of record.[9, 10] Frequent re-evaluations of general principles of management and changes in specific antibiotic therapy have been necessary in order to keep abreast of this changing situation. New antistaphylococcal antibiotics are being developed, and they must be tried clinically in order to establish their relative value among the presently available agents.

Many factors must be considered in the evaluation of the efficacy of any therapeutic program for the management of staphylococcal disease. These include the type of patient infected, the time of the infection, the locality in which the infection occurs, and the site of infection. The age of the host and the efficiency of his defense mechanism are factors which influence the success of treatment. Studies of Finland,[9] Spink,[4] Hinton and Orr,[11] and others have demonstrated changing antibiotic susceptibility of staphylococcal strains in individual hospitals over

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a period of several years. Consequently, results using different types of therapy, even within a single hospital, cannot be compared if the cases occur at widely separated intervals. The locality in which infection occurs also affects the outcome of treatment. Results obtained in patients acquiring their infections outside of the hospital cannot be compared with results in patients with hospital-acquired disease. Studies of "street strains" of staphylococci isolated from patients acquiring disease in the community show these strains to have a different antibiotic sensitivity pattern from those isolated from nosocomial infections.[12]

In addition to differences between strains acquired in hospital and non-hospital environments, there may be differences in hospital-acquired strains depending upon the antibiotics most extensively used by the individual hospital.[13] Therefore, in the discussion of the results of management of any group of staphylococcal infections, the phage types and the antibiotic susceptibilities of the etiologic agents must be clearly defined.

During the two-year period from August, 1956, to August, 1958, approximately 400 children with staphylococcal disease were seen at Jefferson Davis Hospital. The management of 204 of the cases was suitable for analysis. Eighty per cent of the infections were nosocomial and 20 per cent non-hospital acquired. The antibiotic management of these 204 cases has been described briefly in another article.[14] The following article is a more detailed account of the results of the treatment of staphylococcal disease occurring in the pediatric age range over a two-year period of time, in a single hospital, and with the utilization of a variety of currently available antibiotic agents. Broad principles of management based upon experience with this group of patients are outlined.

DESCRIPTION OF CASES

Selection.—The cases selected for study were limited to those occurring in a time interval (1956 to 1958) during which the phage types and antibiotic sensitivities of prevalent strains at Jefferson Davis Hospital were comparable. Only those cases in which the diagnosis was established by identification of the organism and in which there was a minimal follow-up period of one month were included. The latter precaution was necessary in assessing results of therapy since the relapse rate of staphylococcal disease is high, especially in the newborn infant. Children with severe debilitating or neoplastic diseases were excluded from this study.

Age Distribution.—The ages of the patients ranged from 12 hours to 12 years (Fig. 1). There were 155 babies under 2 months of age, 32 infants from 2 months to 2 years of age, and 17 older children. The babies under 2 months of age were further classified as to prematurity or term birth.

Site of Disease.—The forms of disease encountered were superficial skin infections and deep subcutaneous abscesses including breast abscesses, septicemia, pneumonia, gastroenteritis, osteomyelitis, meningitis, otitis media, omphalitis, conjunctivitis, abdominal abscesses, and laryngotracheobronchitis (Table I). Sixty-six of the patients

TABLE I. SITE OF INFECTION AND MORTALITY RATE IN 138 PATIENTS WITH SERIOUS STAPHYLOCOCCAL DISEASE

SITE	NUMBER	DEATHS	PERCENTAGE
Septicemia	40	19	47
Pneumonia	26	5	19
Deep abscess	36	3	8
Gastroenteritis	16	2	12
Meningitis	3	2	66
Miscellaneous	17	2	12
Total	138	33	24

had impetigo or conjunctivitis alone; the other 138 children had more severe involvement. Of the 138 patients with serious staphylococcal disease, 57 had to age is striking (Fig. 2). Fifty-one per cent of the newborn infants (both full term and premature) had disseminated infections. After the age of 2

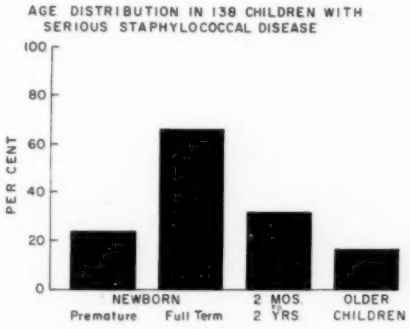

Fig. 1.

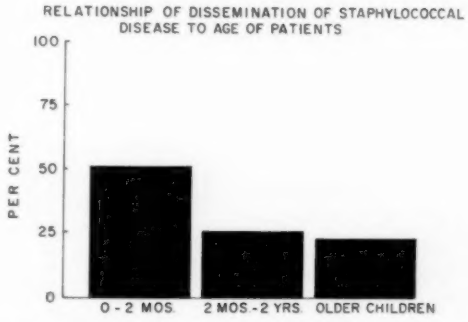

Fig. 2.—Analysis of 138 patients with serious staphylococcal disease.

two or more manifestations of the disease, such as impetigo and pneumonia, impetigo and septicemia, subcutaneous abscess and gastroenteritis. The relationship of degree of dissemination months, the percentage of patients with multiple sites of involvement dropped to approximately 25 per cent.

Description of Organism.—The strains of staphylococci isolated from

this group of patients were tested for antibiotic sensitivity pattern by the disk and tube dilution techniques. Approximately 75 per cent of the strains were phage typed. The organisms infecting the newborn infant showed considerable uniformity in antibiograms and phage types. This was less marked in the organisms isolated from older infants and children. All strains of staphylococci isolated from newborn infants with impetigo and severe forms of disease were of the "hospital strain," a strain resistant to penicillin, streptomycin, tetracyline, and erythromycin. The majority of strains isolated from the newborn infants were phage type 81 (42B/81/-44A/70). Most of the phage type 81 strains showed resistance to penicillin, streptomycin, and the tetracyclines, while 70 per cent were resistant to erythromycin, 50 per cent to chloramphenicol, and 5 per cent to novobiocin. Ninety-five per cent were sensitive to bacitracin and all were sensitive to neomycin. Approximately one-half of the strains were tested against kanamycin and vancomycin and were all sensitive to these two antibiotics.

The organisms isolated from older infants and children were less uniform in their phage types and sensitivity patterns. In this group of 49 strains, 26 were considered to be "hospital strain," 12 were considered to be extrahospital acquired, and 11 were of indeterminate origin. Ten of the 49 strains were penicillin sensitive, 12 streptomycin sensitive, and 15 tetracycline sensitive. It is of interest that epidemic strain 81 was isolated from a severely ill 2-year-old boy who had no known hospital contact. This strain was therefore classified as an outside strain.

Diagnostic Methods.—In superficial infections, such as conjunctivitis and impetigo, direct smear and culture of the lesions were performed. The etiologic agent in most cases of breast abscess, deep subcutaneous abscess, and osteomyelitis was identified from material obtained at the time of surgical drainage. In several instances in which cellulitis resolved without drainage, the specific diagnosis was not verified until dissemination of the organism to other sites was revealed at postmortem examination. In two cases which did not require drainage, the etiologic agent was identified by the presence of an associated staphylococcal bacteremia.

The diagnosis of septicemia due to *Staphylococcus aureus* was a particularly difficult one because of the likelihood of contamination of cultures. Since most of the infants with serious staphylococcal disease had heavy colonization of the nose, throat, skin, and gastrointestinal tract, it was essential to exercise extreme care in obtaining and interpreting results. Both broth and pour plate techniques were carried out on each blood sample. In the patients who died there was a close correlation between the clinical diagnosis of septicemia, results of the postmortem blood culture, and the demonstration of multiple sites of staphylococcal involvement at postmortem examination.

Rigid specifications were met for the diagnosis of staphylococcal pneumonia. The diagnosis was established by one of the following: isolation of the organism from empyema fluid, isolation of the organism from material obtained by lung puncture, using the

technique of Disney and associates,[15] the existence of staphylococcal bacteremia in conjunction with pneumonia, or microscopic evidence of staphylococcal pneumonia at autopsy. Predominance of *Staphylococcus aureus* in the throat even in the older child with pneumonia was not considered valid proof of its etiologic role. The coexistence of pneumatocele and pneumonia was considered suggestive but not diagnostic.

The diagnosis of gastroenteritis due to the staphylococcus was made by the use of the direct smear and culture of the stool. The former was the more reliable procedure since it furnished a rough quantitative estimate as to the relative proportions of the various organisms. Culture of the stool was often misleading because of the inhibitory effect of the Gram negative bacilli upon staphylococcal growth. In many cases culture of the stool showed only Gram negative bacilli, whereas the direct examination of the same specimen revealed Gram positive cocci to be the predominant flora. In addition to the usual media employed for stool culture, blood agar and differential media* were used. In two cases the diagnosis was verified by demonstration of the presence of *Staphylococcus aureus* in perforating abscesses of the bowel at postmortem examination.

The spinal fluid of three patients with meningitis had an increase in cell count, an increase in protein, and a decrease in sugar. The causative agent was demonstrated by both smear and culture.

Management.—Certain broad principles of management were applied to all of these patients. Suspect and isolation areas were provided and techniques of care rigidly enforced. Suspect areas were designated for the housing of patients in which the diagnosis of staphylococcal disease was suspected but not definitely proved. Patients with obvious skin infection and with proved staphylococcal disease were placed in isolation. Special nurses were assigned to these areas, and much of the time a particular physician was assigned to the care of patients in suspect and isolation areas. Optimal nursing and physician care served two functions; namely, it assured the patient the best of care and it protected other patients in the unit.

In addition to close supervision during hospitalization, it seemed necessary to keep the young infants under close surveillance for a period of several additional months. This was accomplished by supplementation of clinic visits with home visits by public health nurses oriented to this problem. A significant number of infants required readmission for either a recurrence of the original manifestation or involvement of another system.

A large number of the children with serious disease had multiple sites of involvement. In many cases it was difficult to decide which site was primary or most significant in the patient's course. In the newborn period particularly, it is almost meaningless to separate a discussion into the entities of septicemia, meningitis, osteomyelitis, and pneumonia, since dissemination is so rapid and frequent. However, since the choice of type of medical or surgical management depends so largely on the major area of involvement, an attempt is made to discuss

*Staphylococcus Medium No. 110, Difco Laboratories, Inc., Detroit, Mich.

the specific methods of management by the major site of disease.

Impetigo.—The 85 cases of impetigo discussed here occurred in newborn infants and were hospital acquired. The age of the patient and strain of the organism influenced the selection of therapeutic agents and, presumably, the outcome. Fifty-six infants had impetigo alone. In this group 36 were treated with chloramphenicol, orally or intramuscularly, 10 received kanamycin intramuscularly and 10 were treated locally. All survived. Twenty-nine babies had impetigo either preceding or occurring simultaneously with more severe forms of staphylococcal disease. Fourteen of the 29 gave a history of pyoderma as the initial manifestation. Two-thirds of the 14 received systemic therapy (chloramphenicol or kanamycin) and one-third received local therapy. This group of patients is too small to make it possible to decide whether or not the use of systemic therapy influenced systemic invasion.

At the present time there are no controlled data available on the safest method of treating impetigo neonatorum due to epidemic strain "81." In our hospital two principles of management, local therapy and close observation of the patient, were carried out in the latter months of this study. Local therapy consisted of the use of sponge bathing with a liquid detergent containing 1 per cent hexachlorophene,* opening of lesions, and application of 1 per cent bacitracin ointment or antibiotic powder† depending on the site of the lesion. "Close observation" of the baby was defined as daily examination of infants seen on an outpatient basis and examination several times per day in hospitalized patients. This examination included close inspection of most commonly involved skin areas, namely, the axilla, the groin, the periumbilical area, the neck, and the areas between the fingers and behind the ears. It also implied observation for spread of infection, either locally or systemically. A close check of feeding, behavior, temperature, and weight gain was maintained. If the local infection progressed or there was suggestion of other types of involvement, either by history or physical examination, intensive systemic therapy was initiated with a bactericidal drug.

It was considered important in the care of the infant with impetigo to control temperature and humidity of the environment since hot, moist skin surfaces appeared to be favorable for spread of infection. Temperature and humidity were maintained as low as was practical. Venepunctures and lancet pricks were reduced to a minimum. Periumbilical and perineal areas were kept scrupulously clean and dry. Moist and abraded areas were dried and protected by the use of antibiotic powder or lotion.* Oiling of the scalp and skin was prohibited. No elective surgical procedures were performed until the infants had been well at least one month.

Conjunctivitis.—The age of onset of conjunctivitis in ten cases was 6 to 13 days with the exception of one infant who developed conjunctivitis on the second day of life. Care was taken to differentiate true infection from

*pHisohex (Winthrop Laboratories, New York, N. Y.) diluted to contain 1 per cent hexachlorophene.

†Neomycin—bacitracin dusting powder: neomycin sulfate 5 mg. per gram and bacitracin 10 mg. per gram in a starch powder base.

*Neomycin—bacitracin shake lotion. Neomycin sulfate 5 mg. per gram and bacitracin 10 mg. per gram in a zinc-oxide base.

chemical irritation due to silver nitrate. The age of the infants eliminated the latter possibility in most instances. All of the cases of conjunctivitis were due to the "hospital strain." Four patients were treated with systemic antibiotics and 6 with local therapy alone. Response to therapy was uniformly good with no marked difference in the length of infection in the two groups. The cases were too few to draw any conclusions as to the necessity for systemic administration of an antimicrobial agent. Duration of therapy depended upon the response. The average length of treatment was one week.

Deep Subcutaneous Abscess.—For simplicity of discussion, the deep subcutaneous abscesses and breast abscesses have been grouped together. There were 36 patients in this group (Table II). Twenty-five were newborn babies with breast abscesses or deep subcutaneous abscesses. The remaining 11 were older infants and children with deep subcutaneous abscesses. Incision and drainage of the abscess was performed in three-fourths of the cases. The others had resolution of the process during antibiotic administration. Twenty-nine of the 36 children were treated with bacteriostatic agents, the majority receiving erythromycin and chloramphenicol or novobiocin, or with a bacteriostatic agent in addition to penicillin or streptomycin (Table II). In this group 3 patients died, all of whom were newborn infants. In 2 of the 3, adequate drainage of the initial staphylococcal lesion was obtained, but superimposed infection due to *Pseudomonas aeruginosa* occurred and the terminal cause of death appeared to be pseudomonas septicemia. In the third patient the area of cellulitis resolved but dissemination and secondary involvement of the lungs developed while the baby was under treatment. Seven patients, 4 newborn babies and 3 older infants, were treated with a single bactericidal agent, kanamycin. Four patients required drainage for abscess formation and three resolved under therapy. There were no deaths on this regime.

Not only was the mortality rate higher in the newborn period than in older infants and children but the morbidity was greater in this age group. The average duration of therapy was two weeks.

TABLE II. RESULTS OF THERAPY IN 36 CASES OF DEEP ABSCESS DUE TO STAPHYLOCOCCUS AUREUS

TYPE OF THERAPY	NUMBER	RECOVERIES	DEATHS
Bacteriostatic agents (erythromycin, chloramphenicol, novobiocin)	29	26	3
Kanamycin	7	7	0

Septicemia.—Forty patients proved to have staphylococcal septicemia (Table III). This included 31 babies less than 2 months of age, 4 in the 2 months to 2 year old group, and 5 in older children. Although initially there was no demonstrable localization of the organisms other than in the blood stream, repeated frequent appraisals of these patients were necessary to detect metastatic abscess formation in the viscera. The most common sites of secondary abscess

formation in patients with primary septicemia were the lungs, bones, gastrointestinal tract, and central nervous system.

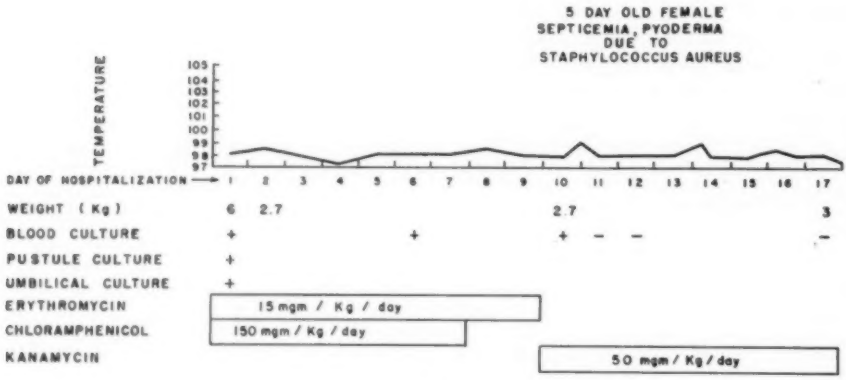

Fig. 3.

involvement in most cases. Frequent urinalyses were performed, especially when patients were being treated with potentially nephrotoxic agents. There was remarkably little evidence of urinary tract involvement due to infection. Because of the silent nature of meningitis in the newborn infant, examination of the spinal fluid was performed routinely. Development of distention and adynamic ileus simulating organic small bowel obstruction occurred frequently and was particularly difficult to treat. In these infants oral feedings were discontinued and attempts made to decompress the bowel. Fluid requirements were fulfilled by parenteral routes. Oxygen was infrequently needed since few patients

Frequent chest examinations by roentgenograms were performed in infants with septicemia since they proved to be especially helpful in the early diagnosis of empyema. However, roentgenographic studies were less reliable in the diagnosis of multiple pulmonary abscesses since many patients with multiple abscesses at postmortem examinations had "normal" roentgenograms shortly prior to death. Bone survey roentgenograms were performed in approximately one-third of the babies with septicemia but close inspection made the diagnosis of bony

TABLE III. RESULTS OF THERAPY IN 40 CASES OF STAPHYLOCOCCAL SEPTICEMIA

TYPE OF THERAPY	NUMBER	DEATHS	PERCENTAGE
Bacteriostatic agent or bacteriostatic agent with penicillin or streptomycin	12	8	67
Bacitracin or bacitracin after failure of bacteriostatic agent	8	3	36
Kanamycin or kanamycin after failure of bacteriostatic agent	16	4	25
Treatment of less than 24 hours	4	4	100
Total	40	19	47

had respiratory distress even in the presence of miliary lung abscesses.

Twelve children were treated with a bacteriostatic agent (erythromycin, chloramphenicol, novobiocin) alone, in combination with another bacteriostatic agent, or in combination with penicillin or streptomycin. Eight of these children died. Eight children received bacitracin initially or bacitracin late after failure of response to bacteriostatic agents. There were 3 deaths in this group. Kanamycin was used in the treatment of 16 patients with 4 deaths. Another 4 children died within 24 hours of admission so that no drug was considered to have had an adequate trial (Table III). Surprisingly, in the patients with septicemia the percentage of deaths was not greatest in the newborn age group. Fourteen of the 31 newborn infants, 4 of the older infants, and one 4-year-old girl died. Analysis of these unexpected figures revealed that each of the older infants was critically ill on admission, with a history of illness of 6 to 10 days' duration without therapy. The 4-year-old girl had blood stream invasion secondary to staphylococcal infection of an 80 per cent second and third degree body burn. Her death was probably due principally to the severity of the burn.

The optimal duration of therapy was difficult to determine. Although the temperature course, white blood cell count, and differential were not helpful in every case, they served as a guide in many cases. Increase in appetite and weight gain were very reliable guides in the young infant. Because of the high relapse rate, the average duration of therapy for septicemia without known localization of organisms in other sites was 3 to 4 weeks.

TABLE IV. RESULTS OF INITIAL THERAPY IN 26 CASES OF STAPHYLOCOCCAL PNEUMONIA

TYPE OF THERAPY	NUMBER	RECOVERIES	FAILURES	DEATHS
Bacteriostatic agent or bacteriostatic agent with penicillin or streptomycin	17	2	15	2
Bacitracin or bacitracin with bacteriostatic agent	6	5	1	1
Kanamycin	1	1	0	0
Treatment of less than 24 hours	2	0	2	2

TABLE V. RESULTS OF TREATMENT WITH BACITRACIN OR KANAMYCIN OF 13 CASES OF STAPHYLOCOCCAL PNEUMONIA WHICH FAILED TO RESPOND TO OTHER ANTIBIOTICS

TYPE OF THERAPY	NUMBER	RECOVERIES	DEATHS
Bacitracin	10	10	0
Kanamycin	3	3	0

Pneumonia.—In an analysis of the 138 cases of serious staphylococcal disease, an attempt was made to differentiate pneumonic involvement secondary to septicemia from a pneumonic involvement which was primary in the respiratory tract. The 26 cases diagnosed as pneumonia fall into the latter group. The majority of these patients were between the ages of 2 months and 2 years. Seventeen of the children were treated initially with a bacteriostatic agent or a bacteriostatic agent

in combination with penicillin or streptomycin (Table IV). Only 2 patients recovered on this therapy, 2 died, and 13 subsequently responded to either kanamycin or bacitracin (Tables IV and V). Six patients received bacitracin alone or in combination with a bacteriostatic agent (Table IV). Five recovered, one died. Kanamycin was used alone successfully in one of the cases of pneumonia (Table IV). The 13 children who failed to respond to bacteriostatic antibiotic treatment were treated with bacitracin or kanamycin (Table V and Figs. 4 and 5). Eleven recovered completely. One of these children developed osteomyelitis of a rib overlying empyema fluid and one had residual atelectasis. Two of the infants developed a fulminating infection at home and were hospitalized such a short time before death that effectiveness of therapy could not be assessed (Table IV).

In the evaluation of the antimicrobial therapy of pulmonary infections, other factors must be considered, namely, the presence of empyema, the method of drainage selected, the type of supportive care given, and the age of the patient.

Seven of the 26 babies had empyema in association with the pneumonic process. Drainage was accomplished in 3 of these by repeated thoracentesis with aspiration of purulent material and instillation of bacitracin. One required closed drainage by means of intercostal insertion of a tube connected to water-sealed drainage. In three instances a single diagnostic thoracentesis was sufficient. The mortality rate of the 26 patients with pneumonia was not influenced by the presence of empyema or the type of drainage used. Decortication was not necessary in any instance. The type of supportive care was similar in all cases. Age seemed to be a factor in the number of deaths. The percentage of deaths was 30 per cent in the neonatal period and 16 per cent in the children from 2 months to 2 years of age. The only older child with staphylococcal pneumonia had an uneventful recovery.

The duration of therapy was 3 weeks to 2½ months. The minimum length of therapy was fixed at 21 days on the basis of the findings of Disney and his associates.[15]

TABLE VI. RESULTS OF THERAPY IN 16 CASES OF STAPHYLOCOCCAL GASTROENTERITIS

TYPE OF THERAPY	NUMBER	RECOVERIES	DEATHS
Bacteriostatic agent	8	6	2
Kanamycin	6	6	0
Neomycin (oral)	2	2	0

Gastroenteritis.—Sixteen patients were treated for staphylococcal gastroenteritis (Table VI). The age range of these patients was from the ages of 1 day to 41 days. There were 2 deaths, 1 in a premature infant and 1 in a full-term baby. Eight patients received a bacteriostatic antibiotic, 6 kanamycin, and 2 oral neomycin. Both deaths occurred in the former group.

As in the septicemia group, adynamic ileus was a difficult problem in the management of gastroenteritis. Feeding was discontinued and measures to relieve distention instituted. Adequate hydration was maintained by use of parenteral fluid.

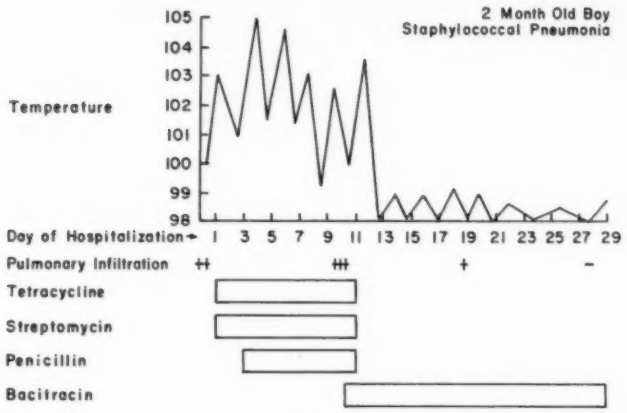

Fig. 4.

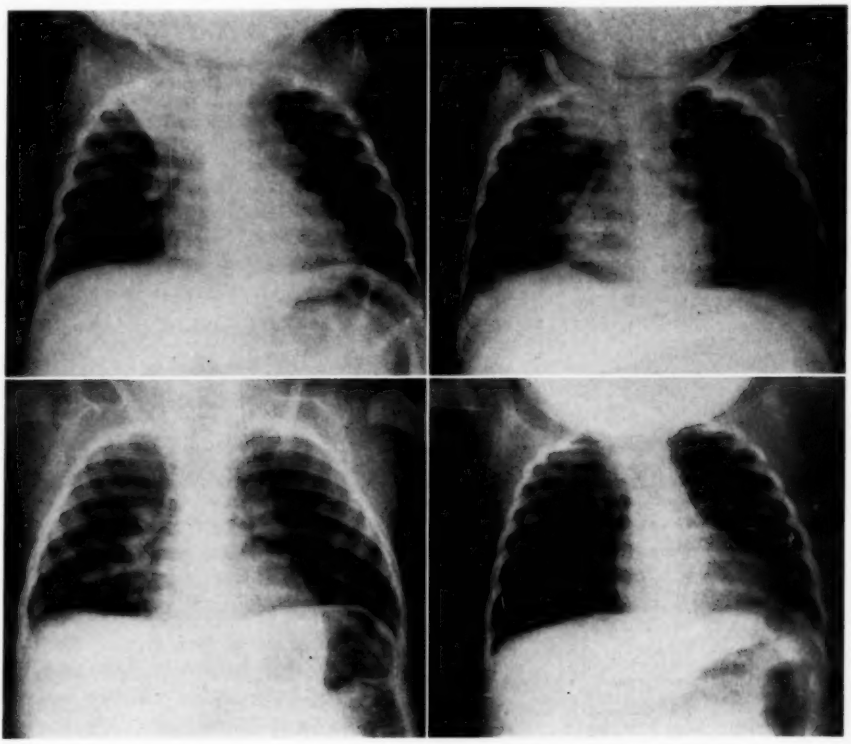

Fig. 5.—Kanamycin treatment of staphylococcal pneumonia in a 12-month-old infant. *a*, Prior to treatment. *b*, Poor response to treatment with bacteriostatic antibiotics, patient critically ill. *c*, Improvement during kanamycin therapy. *d*, After 2 weeks' treatment with kanamycin.

Duration of treatment was individualized, but the average length of antibiotic administration was 14 days.

Meningitis.—Although several patients developed meningitis secondary to septicemia, only 3 presented with meningitis as the major difficulty. All 3 were under 2 months of age and had nosocomial infections. Various combinations of bacteriostatic and bactericidal drugs by intramuscular, intravenous, intratheeal, and intraventricular route were administered. In spite of vigorous therapy only one patient survived. It was possible to sterilize the spinal fluid of another of the babies, but a large walled-off abscess in the frontal lobe was discovered at postmortem examination. The third infant developed hydrocephalus and died.

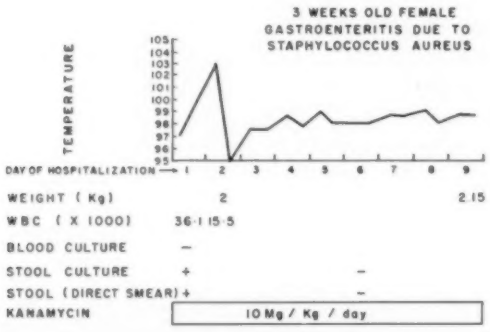

Fig. 6.

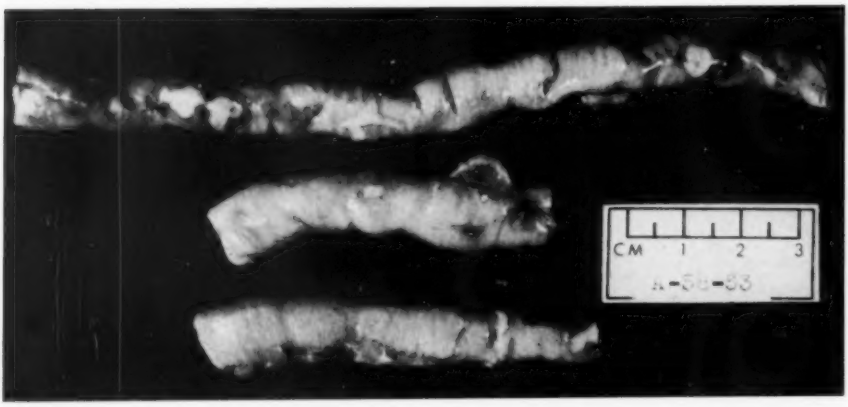

Fig. 7.—Section of the bowel of a 21-day-old infant who succumbed to staphylococcal gastroenteritis. Note perforating ulcers. Suture material can be observed where attempt was made to close one of these at time of surgery 24 hours before death.

Miscellaneous Sites of Involvement.—The 17 patients classified as miscellaneous in Table I had the following types of involvement: osteomyelitis 5, omphalitis 3, otitis media 3, appendiceal abscess 2, retroperitoneal abscess

1, laryngotracheobronchitis 1, ethmoiditis 1, and liver abscess 1. The patient with laryngotracheobronchitis died due to massive edema of the larynx and trachea. The patient with liver abscess had a long-standing disease with inadequate drainage. The remaining 15 patients in this group responded to combined medical and surgical treatment. Response to kanamycin or bacitracin therapy after failure of chloramphenicol, erythromycin, or novobiocin was striking in several instances (Fig. 8).

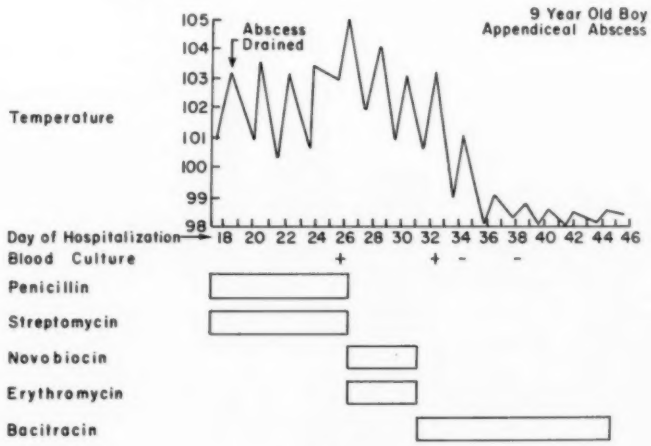

Fig. 8.

Selection of Antimicrobial Agents, Dosage, and Route.—Antimicrobial agents were usually selected on the basis of in vitro sensitivity patterns of the organisms. However, as Wise[16] points out, immediate therapy must be empirical. The first 24 to 48 hours of antibiotic therapy must be planned according to the probabilities of certain antibiotics being effective. Penicillin, the tetracyclines, and streptomycin were not used alone initially in any of these patients, even those considered to have an infection acquired outside the hospital. These antibiotics were used in combination with some other agent until results of in vitro tests were available. After 24 to 48 hours, treatment was adjusted according to the antibiotic susceptibilities of the infecting strain.

The patients with hospital-acquired infections treated during the first year of this study usually received a combination of erythromycin and streptomycin, erythromycin and chloramphenicol, or chloramphenicol or novobiocin alone. Disappointing results using these commonly used antibiotics and increasing awareness that a large proportion of these cases were due to the virulent phage type 81 staphylococcus led to a trial of other antibiotics. Bacitracin and later the new antibiotic, kanamycin, were used. Both of these drugs seemed especially suitable for use in infants and children because of their bactericidal activity and because they could be administered by the intramuscular route.

The dose of the various antibiotics used is outlined in Tables VII and VIII. The concentration of bacitracin in solutions used for instillation was 500 u. per milliliter and that of kanamycin was 2.5 mg. per milliliter. In seriously ill patients all antibiotics were given initially by the parenteral route for a minimal period of 48 hours. Oral therapy was used when the patient began to improve and where it was practical. Local antibiotic administration was used in certain types of localized infections, i.e., empyema,

TABLE VII. BACTERIOSTATIC ANTISTAPHYLOCOCCAL ANTIBIOTICS

DRUG	ROUTE	DAILY DOSAGE (mg./kg.)	INTERVALS (hours)	SIDE EFFECTS*
Tetracyline	Oral	30-50	6	Hypersensitivity; gastrointestinal irritation
	intramuscular	30-50		
	intravenous	30-50		
Chloramphenicol	Oral	30-100	6	Rare bone marrow injury; gastrointestinal irritation
	intramuscular	30-100	6-12	
	intravenous	30-80		
Erythromycin	Oral	20-50	6	Gastrointestinal irritation
Novobiocin	Oral	20-50	6	Hypersensitivity reactions
	intravenous	20-30		
Oleandomycin	Oral	20-50	6	Gastrointestinal irritation
Ristocetin	intravenous	25-200	6-8	Skin rash; thrombophlebitis

*Side effects as reported in literature.

TABLE VIII. BACTERICIDAL ANTISTAPHYLOCOCCAL ANTIBIOTICS

DRUG	ROUTE	DAILY DOSAGE (mg./kg.)	INTERVALS (hours)	SIDE EFFECTS*
Penicillin G (aqueous)	intramuscular	20,000-50,000 U./kg./day	3-6 or continuous	Hypersensitivity reactions
	intravenous	20,000-50,000 U./kg./day	intravenous	
Streptomycin	intramuscular	20-50	8	Eighth cranial nerve damage; hypersensitivity reactions
Bacitracin	intramuscular	600-1200 U./kg./day	6	Nephrotoxicity; pain on injection; eosinophilia
Neomycin	intramuscular	10-15	6-12	Nephrotoxicity; ototoxicity
Vancomycin	intravenous	50-100	6	Local thrombophlebitis; skin rash
Kanamycin	intramuscular	10-50	6-12	Rare ototoxicity; nephrotoxicity (?)

*Side effects as reported in literature.

purulent pericarditis, meningitis, and septic arthritis.

Results.—The results of treatment have been discussed under each entity. In summary, all of the patients with conjunctivitis and impetigo alone recovered, 103 of the 138 more seriously ill patients recovered, 2 were left with residual involvement, and 33 died (Table I). The greatest number of deaths was in the newborn age group (Fig. 9) and in patients with the diagnosis of septicemia (Table I).

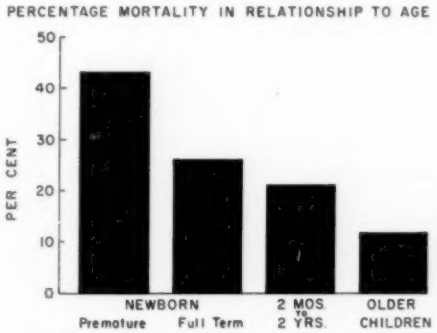

Fig. 9.—Analysis of 138 patients with serious staphylococcal disease.

Age distribution, surgical drainage, supportive therapy, and other factors influencing recovery have been discussed by site of infection. There seemed to be no marked difference in the distribution of these variables among the patients who received bacteriostatic agents and those who received kanamycin or bacitracin. Results, however, were significantly different in these two groups. The mortality rate in all types of seriously ill patients treated with bacteriostatic drugs or bacteriostatic drugs in combination with penicillin or streptomycin was 22 per cent. The mortality rate in the patients treated with kanamycin or bacitracin either alone or in combination with a bacteriostatic drug was 13 per cent. This difference is even more striking when it is considered that in many cases kanamycin and bacitracin were not used until the pathologic process had progressed during other treatment and the patient had become critically ill.

Untoward side effects were remarkably infrequent. The usual side effect of gastrointestinal irritation observed in the use of erythromycin, chloramphenicol, and the tetracyclines was difficult to evaluate in patients having diarrhea and vomiting as part of the disease process. In patients with no antecedent gastrointestinal difficulty, gastrointestinal irritation was not marked.

Novobiocin was administered to 20 patients with one toxic reaction. The reaction, urticaria and a diffuse morbilliform rash, promptly subsided when the drug was discontinued. There were no penicillin or known streptomycin reactions in this group of patients.

Bacitracin was used very cautiously, although nephrotoxicity is reported to be less in children than in adults.[17] Blood urea nitrogen values were obtained prior to, and twice weekly

during, the course of treatment. Urinalyses were performed prior to treatment, on alternate days during bacitracin therapy, and several days post-therapy. In only one of 27 patients treated with bacitracin was the blood urea nitrogen significantly elevated. In this patient it returned to normal after discontinuation of the drug. A second course of bacitracin was subsequently given to the same individual with no ill effects. Microscopic examination of the urine revealed cylindruria rather consistently on the sixth to ninth days of bacitracin administration. This was a transient phenomenon, and casts disappeared from the urine without reduction of the drug dosage. Proteinuria was present in many of the seriously ill patients but was not sufficiently increased by administration of bacitracin to warrant discontinuation of the drug. None of the patients treated with bacitracin had any clinically obvious residual renal damage. Renal function tests were not performed. Three patients receiving bacitracin had marked eosinophilia ranging from 21 to 45 per cent. This, too, was reversible when the drug was discontinued.

Thirty-six kanamycin-treated patients were subjected to a similar observation of renal status. Blood urea nitrogen determinations were performed prior to, and twice weekly during, therapy and for several weeks after therapy. Daily microscopic examinations of the urine were performed. In no instance was the blood urea nitrogen elevated above the level associated with the original disease. Coarse granular casts were observed in most patients receiving as much as 50 mg. per kilogram per day of kanamycin. Casts disappeared promptly when the dosage was lowered or the drug discontinued. Reports of eighth cranial nerve toxicity following kanamycin administration prompted appraisals of hearing acuity in older infants and children. No deficit was noted on physical examination. A 12-year-old boy who had received 35 to 50 mg. per kilogram per day for 95 days had no gross hearing loss. A 6-year-old girl who received 15 to 50 mg. per kilogram per day had normal hearing on audiometric testing. In the newborn infants assessment of hearing was not possible.

Failure of therapy was considered to be due to late institution of therapy, poor host response, improper selection of antimicrobial agent, localization of infection in a site inaccessible to adequate drainage, and irreversible tissue damage. The two latter causes of failure may represent results of institution of therapy after the disease had become advanced.

DISCUSSION

The importance of two factors, the source of the infection and the type of host, in the evaluation of any therapeutic program for staphylococcal disease has already been mentioned. In general it was felt that infections acquired outside of the hospital were, as a group, less difficult to treat than the nosocomial ones. The factor of environment in which the infection was acquired cannot be considered alone, however, since the extrahospital infections tended to occur in older children and hospital-acquired infections were most common in the most vulnerable subject, the newborn infant. Hospital-acquired disease was usually severe and difficult to manage. The severe nature of the

pathologic processes encountered posed the question of whether the use of large amounts of antibiotics at Jefferson Davis Hospital had permitted the emergence of highly resistant strains of staphylococci. Not only had antibiotics been used extensively in this general hospital for the treatment of patients of all ages, but unusually large amounts of antibiotics had been used in the pediatric age group because of recurrent staphylococcal outbreaks in the newborn infants' nurseries. As has been stated, the majority of strains infecting newborn infants were epidemic type 81 and were resistant to penicillin, tetracycline, streptomycin, and erythromycin. These strains were similar to those found by Blair and Carr[18] to be predominant from 1954 to 1957 in a cross-section survey of organisms in hospitals in the United States. According to these authors, the staphylococcus of phage type 80/81 appears to be possessed of more than ordinary virulence and is easily disseminated both within the hospital community and within the individual patient. It now appears that in spite of the duration and magnitude of the staphylococcal problem at Jefferson Davis Hospital and the extensive use of antibiotic agents, the types of staphylococcal infection encountered at this hospital are not unique to its antibiotic environment but comparable to those seen in similar institutions at the present time.

The influence of the condition of the host (age and degree of maturity) upon the course of staphylococcal disease is clearly evident from the data presented here (Figs. 2 and 9). Morbidity, mortality, and relapse rate were all higher in the newborn age group than in older infants and children. The mortality rate in premature infants was significantly higher than in the full-term newborn infants or in older children (Fig. 9). The inability of the newborn child to localize staphylococcal infection is shown by the percentage of newborn babies with disseminated disease as compared to the percentage of older infants and children with multiple sites of involvement (Fig. 2). The reasons for this atypical response of the young infant are not well understood. Rammelkamp and Lebovitz[19] in studying the role of coagulase in staphylococcal disease observed a difference in the concentration of reacting factor in the sera of adults, older children, and infants. In infants small amounts were the rule and these amounts were shown to increase with age. This poses an interesting and not entirely academic question as to whether this may be one of the factors in the newborn infant's inability to localize infection.

The initial site of infection and duration of infection prior to treatment had a direct relationship to outcome. The mortality rate was seen to be highest in patients with septicemia, regardless of the age of the patients (Table I). The duration of infection before institution of therapy, of course, influenced response to treatment. Effective levels of antibiotic substances are much more easily obtained in the stage of cellulitis than later when the pathologic process has progressed to abscess formation. Also, if the process is allowed to progress, the necrotizing nature of the organism may cause tissue damage to vital structures. In several instances where treatment was begun late in the course of the disease, the infection was brought under control but tissue damage was irreversible.

In a recent discussion of staphylococcal infections in children, Koch and Donnell[20] reported a high degree of correlation between clinical response and antibiotic therapy selected on the basis of in vitro testing of the etiologic agent. Correlation was less evident in our series. The in vivo response was relatively predictable in older infants and children, but there was less correlation between the in vitro antibiotic sensitivity pattern and patient response in the newborn infant age group. In many instances the pathological process continued to progress in newborn babies receiving bacteriostatic drugs which by laboratory guides should have been effective. Others showed an initial response but later had a recurrence of the infection. The lack of correlation in the very young may represent the lack of host-immune response. In addition to the in vitro sensitivity of the infecting strain, the age and condition of the host must always guide one's selection of therapy.

In spite of this incomplete correlation, it is essential that in vitro testing be carried out in all cases of serious staphylococcal infections. It is of aid not only in planning a therapeutic program for the individual patient but it is important in following trends in the emergence of resistant strains in the hospital and community. Knowledge of the antibiotic sensitivity patterns and phage types of predominant strains during outbreaks at Jefferson Davis Hospital was a factor in the reduction of morbidity and mortality.

In the description of the treatment of the 204 children in this study, erythromycin, chloramphenicol, novobiocin, and the tetracyclines have been referred to as "bacteriostatic" and penicillin, streptomycin, Kanamycin, and bacitracin as "bactericidal." They are classified under these two modes of action upon staphylococci in accordance with the data of Wise[16] and Yow and Monzon.[21] Wise states that the importance of the bactericidal activity of an antibiotic in therapy is not well understood since these effects are not commonly determined and, therefore, correlations are unknown. The results of the therapy of the 138 children with serious staphylococcal disease in this study seem to indicate a definite relationship between bactericidal activity and efficacy of therapy, particularly in patients with poor defense mechanisms and in patients with large numbers of infecting organisms. Analysis of results of treatment in our series shows kanamycin and bacitracin to be highly effective against the staphylococcus both in vitro and in vivo. As in the use of any drug, the danger of the potential toxicity of these agents must be weighed against the seriousness of the patient's illness. Vancomycin is bactericidal for the staphylococcus in vitro, and good results have been reported following its use.[22] However, vancomycin was used infrequently in this series of patients because of the difficulties involved in long-term administration of the drug intravenously in the pediatric age group. The same problem limited the use of ristocetin. Neomycin is a powerful antistaphylococcal drug but was not used because of its marked toxicity.

Emergence of strains of staphylococci resistant to kanamycin and bacitracin was not a problem in the individual patient while under treatment. Strains of staphylococci isolated from the hospital community also

remained sensitive to these two antibiotics during the period of this study. Conceivably, the predominant strains in hospitals using these antimicrobial agents may eventually prove to be resistant to kanamycin and bacitracin. However, since these antibiotics are potentially toxic and must be administered by the parenteral route, it is unlikely that they will be used indiscriminately. If emergence of resistant strains occurs, it will probably be at a much slower rate than has been experienced in the use of the more widely administered antibiotics.

SUMMARY AND CONCLUSIONS

1. Analysis of the management of 204 cases of staphylococcal disease in infants and children is presented. Sixty-six of these patients had mild disease and 138 had moderately severe or severe involvement. Eighty per cent of the infections were hospital acquired and 20 per cent were nonhospital acquired.

2. Age of the patient influenced morbidity and mortality. In the 138 patients with serious staphylococcal disease, the mortality rate was 43 per cent in the premature infants, 26 per cent in the full-term newborn infants, 21 per cent in children from 2 months to 2 years of age, and 11.7 per cent in older children. The degree of dissemination was related to the age of the patient, demonstrating inadequacy of host defenses in the young infant.

3. The management of staphylococcal disease in the young infant differs from that in the older child. All staphylococcal infections must be considered potentially serious in the young infant because of the atypical manifestations and unpredictability of the course of staphylococcal disease in this age group. In the older child superficial infections may be safely treated with local therapy. However, controlled studies are needed to establish the best method of management of infants with superficial infections, such as impetigo neonatorum and conjunctivitis, now that the majority of these infections are due to the highly invasive strain 81. Regardless of the choice of antimicrobial agent and its route of administration, close surveillance of these patients is necessary. Moderately severe infections, such as deep subcutaneous abscesses, occurring in the older child can be expected to respond to bacteriostatic antistaphylococcal drugs and local care. Subcutaneous abscesses and breast abscesses occurring in the young infant should be treated with a bactericidal antistaphylococcal drug and local care. The prognosis of severe staphylococcal disease in all age groups is so grave that intensive treatment with a bactericidal antibiotic or a combination of a bactericidal drug and a bacteriostatic drug is indicated.

4. Adequate incision and drainage are essential because of the ability of the staphylococcus to remain viable within abscesses. In instances where it is difficult to insure adequate drainage, it may be advisable to instill a bactericidal antibiotic directly into the infected cavity. In infants, in other individuals who handle infection poorly, and in patients with undrained localized infections, it is necessary to continue therapy for a prolonged period in order to prevent relapses of infection.

Disk and tube dilution tests for antibiotic susceptibility of the strains of staphylococci were performed by the Jefferson Davis Hospital Laboratory, The Ben Taub

Infectious Disease Laboratory, and the Houston City Health Department Laboratory, Houston, Texas. Phage typing studies were conducted by Dr. J. V. Irons, Bureau of Laboratories, Texas State Board of Health, Austin, Texas.

Kanamycin was provided by the Bristol Laboratories, Syracuse, N. Y. and Multidisks were supplied by Consolidated Laboratories, Inc., Chicago Heights, Ill.

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CYSTIC LESIONS OF THE KIDNEY IN INFANTS AND CHILDREN

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ALTHOUGH renal cysts of various types are relatively infrequent in early life, their proper identification is important both prognostically and therapeutically. Unfortunately, analogous terms have been applied to quite dissimilar cystic lesions of the kidney, and in many instances the term polycystic disease has been employed to refer to any kidney containing multiple cysts. As a result, attempts to determine such features as the incidence, familial nature, clinical manifestations, and even the histologic pattern of a specific type of renal cystic lesion are rendered extremely difficult. The present paper is offered in an attempt to delineate the various cystic lesions of the kidney encountered in infants and children and to clarify the clinical, roentgenographic, and pathologic manifestations associated with specific types of lesions.

One or more small cortical cysts are commonly demonstrable histologically in the kidneys of newborn infants. There is no significant increase of connective tissue about the periphery of these cysts, which may result from slight dilatation of either tubules or glomerular spaces. They are of no clinical significance.

RENAL CYSTS WITH TUBEROUS SCLEROSIS

Renal lesions of various types are commonly present in patients with tuberous sclerosis. Multiple hamartomatous nodules varying from microscopic size to large bulky growths may be present in both kidneys. In addition small cysts up to a few millimeters in diameter may be scattered through the renal cortex. These are lined by low dark-staining cuboidal epithelial cells or by larger cells with abundant cytoplasm. Slight papillary proliferation of the epithelial elements within these cysts may be noted, and they may or may not be surrounded by a distinct stroma of connective tissue. Defectively developed glomeruli, "inclusions" of fat or of large pale epithelial cells within the glomeruli, and mesenchymal hamartomas with various patterns may also be encountered.[1] Although clinical evidence of renal disease in patients with tuberous sclerosis is usually absent, rarely the involvement may be so extensive as to lead to uremia. A tumor which was reported to be a hypernephroma has been described in a 10-year-old boy with tuberous sclerosis.[2] Renal tumors associated with tuberous sclerosis usually behave in a benign manner, and this patient was well 3½ years later.

SIMPLE CYSTS

Simple cysts of large size are predominantly lesions of adult life but have been observed in infants and children.[3-6] Although clinically they are usually solitary and unilateral and

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thus have been referred to as solitary cysts, they may be bilateral[7] or more than one cyst may be present in one kidney.[8, 9] The presenting complaint is usually that of an abdominal mass unassociated with abnormal findings in the urine. Characteristically the cysts do not communicate with the renal pelvis and do not fill with contrast medium during intravenous pyelography. Pyelograms may be normal or may reveal a filling defect in the renal pelvis; a crescent-like deformity of the border of the calyx adjoining the cyst is probably the most characteristic

Fig. 1.—Pyelogenic cyst in the kidney of a full-term stillborn fetus. Note the narrow isthmus connecting the cyst with the renal pelvis.

roentgenographic finding but a variety of patterns may be observed, depending upon the size and location of the cyst.

Simple cysts are unilocular and their walls are composed of fibrous tissue which may be lined by low cuboidal or flattened epithelium. In some instances, however, no epithelial lining is demonstrable. Since they are sharply demarcated from the adjoining renal parenchyma, they can usually be resected and do not necessitate removal of the affected kidney.

PYELOGENIC CYSTS

Pyelogenic cysts or calyceal diverticula are cystic cavities lined by transitional epithelium continuous with that of a renal calyx. They are usually small and communicate with the calyx through a narrow isthmus. Although some calyceal cysts are undoubtedly congenital in origin (Fig. 1), others probably occur secondary to some other renal lesion, e.g., calculus or chronic pyelonephritis.[8] Differentiation of congenital and acquired pyelogenic cysts may be impossible. Although frequently asymptomatic, pyelogenic cysts may harbor infection and favor the formation of calculi, with resulting renal colic and hematuria.[10] They may be outlined by excretory or retrograde pyelography, and in the absence of secondary infection the contrast medium is usually rapidly emptied from their lumen. Pyelogenic cysts do not require surgical extirpation unless they are responsible for clinical manifestations or for persistent or intermittent pyuria.[11]

PERINEPHRIC CYSTS

Encysted collections of fluid which more or less surround the kidney have been referred to by a variety of terms, including perirenal hydronephrosis, hygroma perirenalis, pararenal pseudohydronephrosis, and perinephric cysts. They are very rare lesions and have been observed less frequently in infants and children than in adults. Certain of these cysts result from perinephric extravasations of urine, the fluid accumulating either beneath the renal capsule or in the surrounding adipose tissue. Urinary obstruction is an important predisposing factor in the

development of these lesions. In other instances perinephric hematomas, either traumatic or spontaneous in origin, may become encapsulated and their contents replaced by clear fluid. The origin of still other perinephric cysts is obscure[12]; many of these are associated with hydronephrosis secondary to ureteral obstruction. Rare perinephric cysts are lined by epithelium and may communicate with the renal pelvis; these have been attributed to remnants of the wolffian duct.

Perinephric cysts manifest themselves by the presence of a palpable abdominal mass associated with abdominal pain. The clinical manifestations may suggest a Wilms's tumor; there may be an associated hypertension.[13] The results of urographic studies vary, depending upon the size and location of the cyst and the presence or absence of hydronephrosis. The renal parenchyma, which is interposed between the cyst and the hydronephrotic renal pelvis, may be so atrophic as to fail to excrete the contrast medium. The pyelographic findings are usually interpreted as being compatible with complete obstruction at the ureteropelvic junction. Treatment consists of excision of the cyst and if necessary of the damaged kidney. Drainage of the cyst prior to its removal is advocated by some.

PARAPELVIC CYSTS

Parapelvic cysts are rare lesions located adjacent to the renal pelvis with which they do not directly communicate. They are usually small and may be multiple and bilateral; rarely they may be large enough to produce a deformity of the renal pelvis and calyces.[14] Parapelvic cysts have been attributed to lymphatic ectasia[15] and are usually incidental findings at autopsy. They appear to be lesions of adult life.

MULTILOCULAR CYSTS

Multilocular cysts are rare unilateral lesions which should be differentiated from simple cysts, from the multicystic kidney, and from polycystic disease of the kidney. The presenting complaint is that of an abdominal mass[16] which may be interpreted as a Wilms's tumor.[17] Characteristically the mass does not communicate with the renal pelvis.[18] Pyelography reveals distortion of the renal pelvis which may be indistinguishable from that produced by a Wilms's tumor.

These are localized multilocular cystic structures, the cavities of which are separated from each other by septums composed of compact fibrous tissue which may contain remnants of renal tubules and glomeruli[19] as well as bundles of smooth muscle. The cysts are usually lined by columnar, cuboidal, or flattened epithelium. The cystic mass may be completely enclosed within compressed renal parenchyma or it may extend into the subcapsular zone of the affected kidney (Fig. 2).

The multilocular nature of the cystic mass, the frequent presence of prominent epithelial cells lining the cysts, and in some instances the occurrence of bundles of smooth muscle in the septums between the cysts tend to differentiate these lesions from simple cysts of the kidney. In contrast to the multicystic kidney the renal parenchyma adjoining a multilocular cyst is normal except for evidence of atrophy secondary to compression by the mass. In contrast to

polycystic disease of the kidneys the multilocular cyst is localized rather than diffuse and is not bilateral.

The nature of multilocular cysts of the kidney is not entirely clear, and some authors do not differentiate between these and simple cysts of the kidney. They are benign lesions which are probably best interpreted as cystic hamartomas, although some have considered them as actual benign neoplasms.[18] Since they are sharply delineated from the adjoining renal parenchyma, they might be surgically resected were the diagnosis to be established prior to nephrectomy. Usually, however, a nephrectomy is performed since the lesion is thought to be a Wilms's tumor.

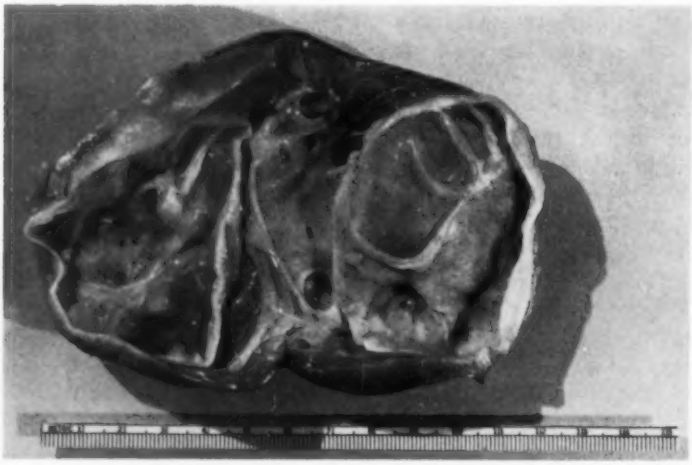

Fig. 2.—Multilocular cyst of the kidney. The renal parenchyma has been sectioned, exposing the renal pelvis and the multilocular cyst. Note the intact renal parenchyma at the upper and lower poles of the kidney. The cyst does not communicate with the renal pelvis.

RENAL HYPOPLASIA

Hypoplastic kidneys may be unilateral or bilateral. They vary considerably in their macroscopic and histologic appearance and cysts need not be present. Clinical manifestations are usually absent when only one kidney is hypoplastic, but infrequently there is an associated hypertension. The ureter on the affected side usually empties normally at the trigone, so that the diagnosis cannot be established by cystoscopy alone. In those instances in which there is simply a quantitative diminution of renal parenchyma, urine of apparently normal quality may be passed from the ureter on the affected side, but death from uremia may ensue following removal of the opposite kidney.[20] The pyelographic changes associated with renal hypoplasia vary considerably in different instances. These include complete absence of opacification of the pelvis and calyces (as in the usual unilateral multicystic kidney), a rudimentary pelvis with small calyces, or a relatively large pelvis as compared with the renal mass. The roentgenographic appearance may simulate that encountered when only the upper pelvis is filled in a kidney with a double pelvis.

Bilateral renal hypoplasia of an extreme degree results in death shortly after birth. In some instances the facies of these infants may suggest that described in infants with bilateral renal agenesis.[21] Less severe forms of bilateral renal hypoplasia may be compatible with life for months or even years. The manifestations are those of chronic renal insufficiency, i.e., stunting of growth, difficulty in feeding, anemia, polyuria with a low specific gravity, hyperphosphatemia, rachitic-like changes in the bones, and azotemia.

Urethral obstruction occurring during intrauterine life is commonly associated with the presence of multiple renal cysts[22] (Fig. 3). Whether or not these are associated with an actual impairment of renal development, i.e., renal hypoplasia, is not entirely clear but their histologic appearance suggests such an association (Fig. 4).

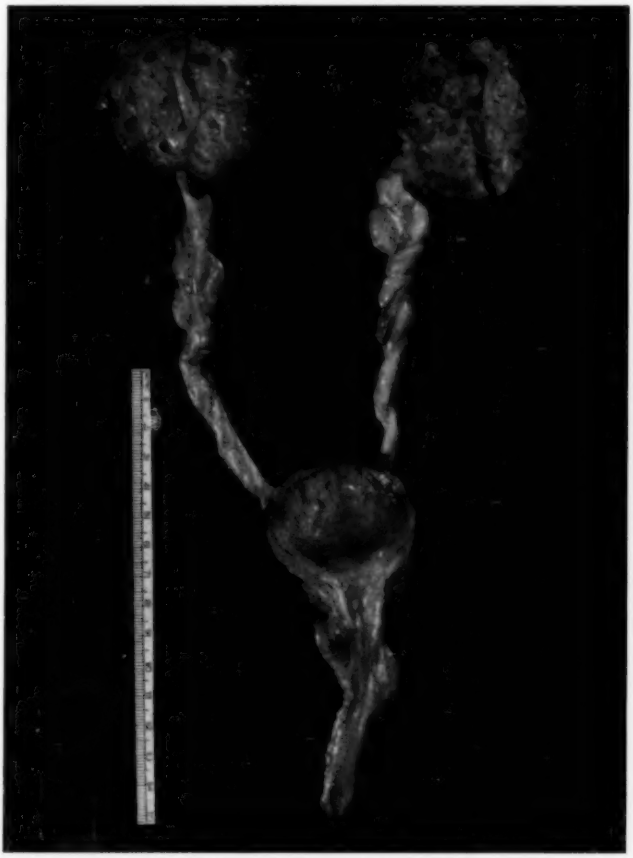

Fig. 3.—Multiple renal cysts associated with bilateral hydronephrosis and hydroureters in a male infant 28 days of age. The histologic appearance of these kidneys is that of renal hypoplasia.

The hypoplastic kidney may differ from normal only quantitatively and may reveal no abnormalities histologically. In such instances the diagnosis is dependent upon the demonstration of decreased numbers of renieuli, only 1 to 5 pyramids being present instead of the normal 12 to 14. In infants with bilateral renal hypoplasia of this type who survive for some time, the renal tubules may be dilated to cyst-like proportions, apparently as a result of functional hypertrophy.[23, 24]

In other instances the hypoplastic kidney is decreased in size (Fig. 5) and its histologic appearance is greatly altered from normal. The renal pelvis may be relatively large as compared with the amount of renal parenchyma. Scattered small cysts are present, and histologically the kidney consists of islands of normal or hypertrophic renal parenchyma alternating with areas of fibrous tissue containing small cysts and a few glomeruli. Islands of hyaline cartilage are commonly present,[25] and the smaller cysts are frequently surounded by concentric rings of primitive connective tissue or smooth muscle (Fig. 6). Advanced degrees of the latter type of renal hypoplasia merge imperceptibly with the multicystic kidneys to be described. Bilateral hypoplastic kidneys containing multiple cysts of varying size have been referred to as bilateral multicystic kidneys.[26] Moreover, a large "multicystic" kidney on one side is in some instances associated with a small hypoplastic kidney on the opposite side (Fig. 7). Thus, although there appears to be some justification

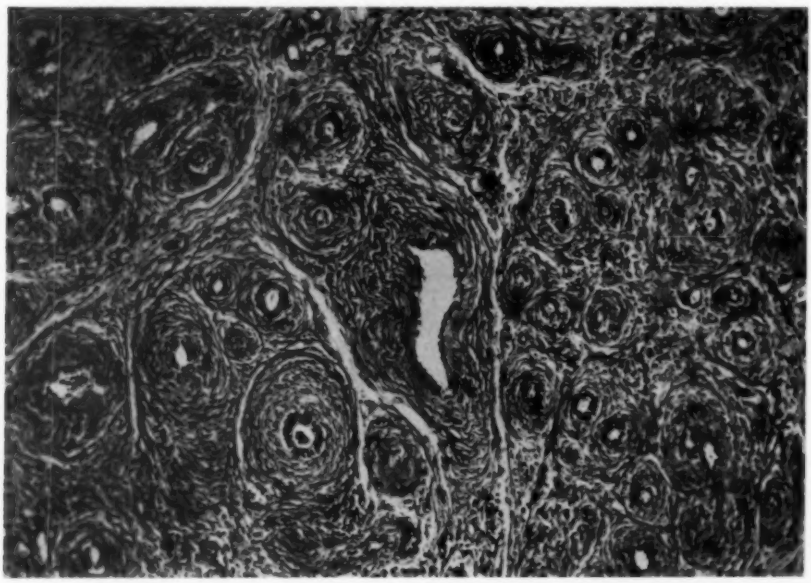

Fig. 4.—Photomicrograph of one of the kidneys depicted in Fig. 3. Note the multiple tubular spaces lined by epithelium and surrounded by concentric rings of mesenchymal tissue (×153).

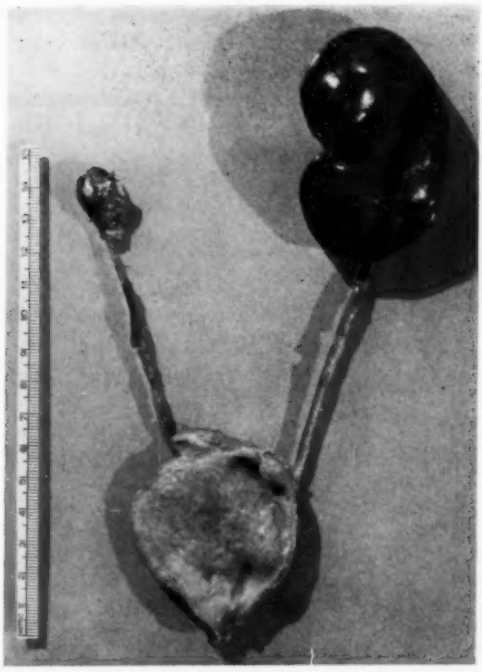

Fig. 5.—Hypoplasia of the right kidney in an infant 22 months of age.

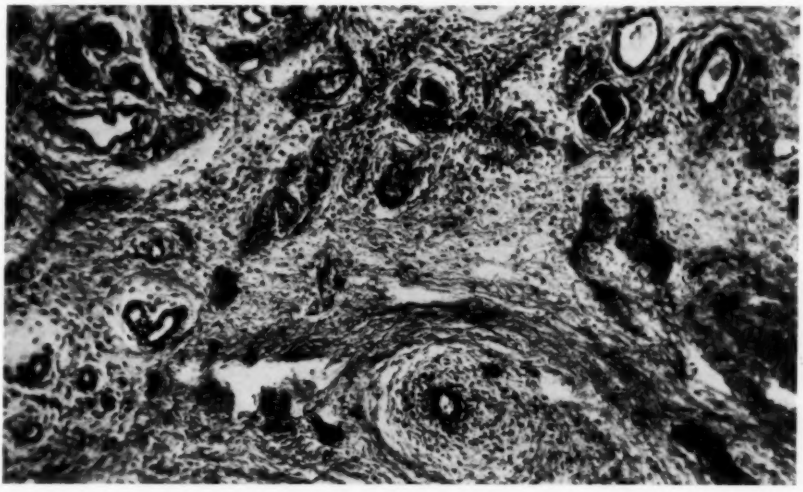

Fig. 6.—Renal hypoplasia. Note the abundant connective tissue containing scattered tubules and at least one glomerulus. Concentric rings of mesenchymal tissue are present about the tubule in the lower part of the photomicrograph (×142).

for retaining the term unilateral multicystic kidney as a descriptive one, it should be recognized as a form of renal hypoplasia.

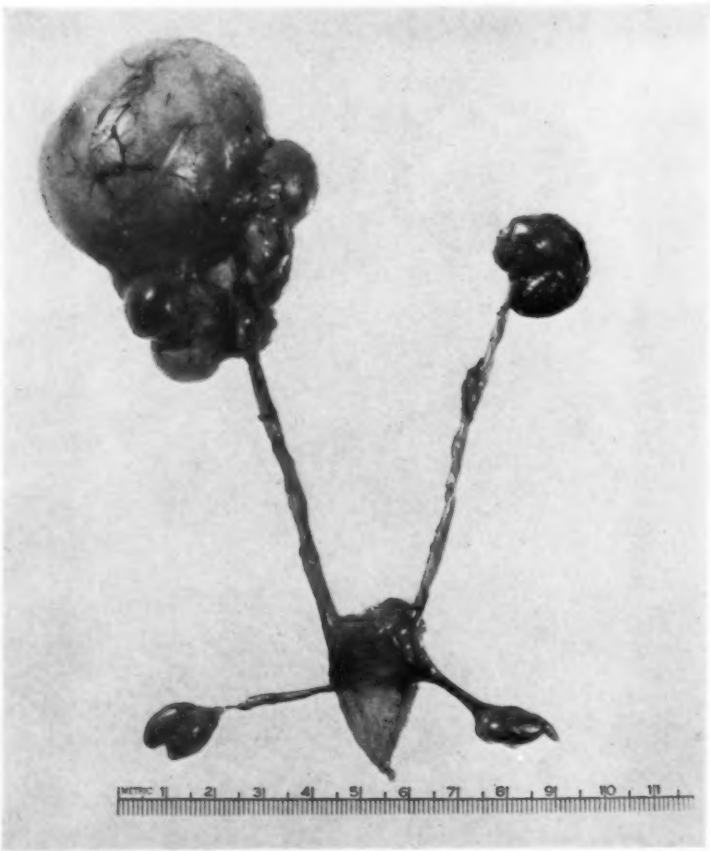

Fig. 7.—Bilateral renal hypoplasia in an infant 13 hours of age. The left kidney is small, whereas the right is large and is replaced by multiple cysts. Compare the right kidney with the unilateral multicystic kidney shown in Fig. 8.

Unilateral Multicystic Kidney.—This is a type of renal hypoplasia and is the lesion which has most frequently been interpreted as unilateral polycystic disease of the kidney.[27-29] It is not familial. The clinical manifestations are those of an abdominal mass in an otherwise healthy infant. The mass is large, lobulated, nontender, and movable. Rarely vomiting and abdominal distention or pain in the renal area have been observed.[30] Urinalyses are normal, although in one rather atypical instance, in which a mass was not palpable, transient pyuria was noted.[31] Intravenous pyelography characteristically reveals complete absence of contrast medium

on the affected side with a normal-appearing collecting system on the opposite side. Rarely a displaced renal pelvis may be visualized on the affected side,[29, 32] and ringlike shadows of calcific density have been observed in a few adults.[30] The ureteral orifice on the affected side may be absent, or attempted retrograde pyelographic studies may demonstrate a small but patent distal ureter which terminates blindly below the ureteropelvic junction. Since the lesion occurs predominantly in infants, the preoperative diagnosis is usually that of Wilms's tumor or hydronephrosis.

Macroscopically the kidney is replaced by a large mass no longer resembling a kidney, composed of multiple cysts of varying size united to each other by loose connective tissue (Fig. 8). As a rule, no renal pelvis can be recognized, and the proximal ureter is usually imperforate. Rarely, however, a hydronephrotic pelvis is present.[28, 33] The cysts are lined by cuboidal or flattened epithelium surrounded by connective tissue or smooth muscle (Fig. 9). Islands of immature renal tissue with a few glomeruli[34] as well as islands of cartilage may be present. The opposite kidney is normal or may reveal evidence of compensatory hypertrophy.

The multicystic kidney should be differentiated from true polycystic disease of the kidney in infants. In the latter, which is almost always bilateral, the reniform shape of the kidneys is retained, the renal pelves are present although they may be distorted, and myriads of cysts of relatively uniform size are separated from each other by more or less intact renal parenchyma. The multicystic kidney, on the contrary, is characteristically unilateral. The affected kidney lacks any resemblance to a normal kidney. The renal pelvis is absent, and the kidney is replaced by a lobulated mass composed of relatively small numbers of cysts of varying size separated from each other by loose connective tissue.[35, 37]

Fig. 8.—Unilateral multicystic kidney removed from an infant 8 days of age.

The prognosis would appear to be excellent in unilateral multicystic kidney,[36] both for the patient and for subsequent siblings, in contrast to true polycystic disease of the kidney which is a genetically determined defect.

POLYCYSTIC DISEASE

The term polycystic disease of the kidney is often applied to any kidney containing multiple cysts. However, as noted above, cysts may occur in one or both kidneys in a variety of conditions. Although descriptively the term polycystic disease is quite applicable to any kidney containing multiple cysts, little would appear to be gained by including all such kidneys in this

single category. Instead, the term polycystic disease of the kidney might better be limited to the genetically determined, familial form of disease, to which the remaining discussion will be limited.

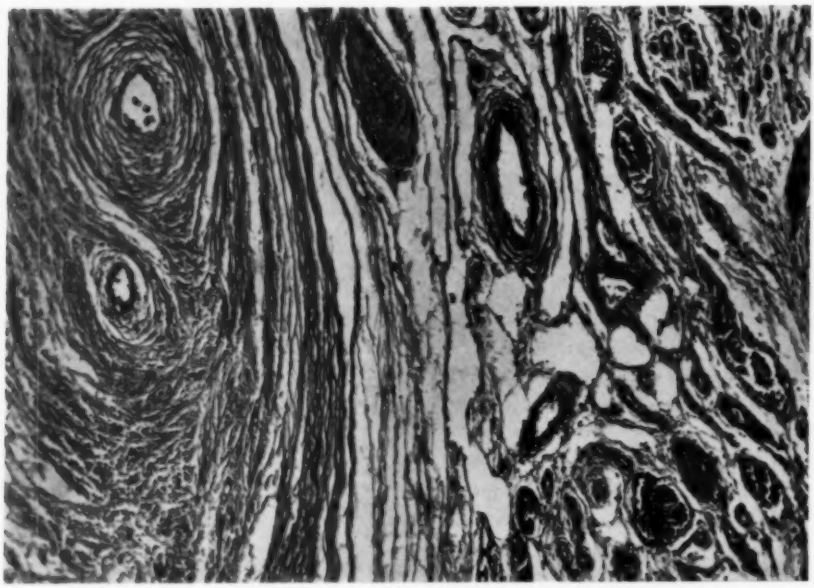

Fig. 9.—Photomicrograph of the unilateral multicystic kidney depicted in Fig. 8. Compare with the photomicrographs of other hypoplastic kidneys, i.e., Figs. 4 and 6.

Polycystic kidneys are almost always bilateral. Whether a unilateral form of true polycystic disease of the kidneys occurs is impossible to state, since it is often impossible to determine the exact nature of the lesions described in the literature. The majority of unilateral "polycystic" kidneys which are reported probably represent instances of unilateral multicystic kidney. Polycystic kidneys in infants are uniformly enlarged, at times to such an extent as to interfere with delivery. The kidneys retain their usual reniform shape and their surfaces are relatively smooth with normal appearing fetal lobulations. In many instances the myriads of minute cysts which are present do not appreciably alter the external surface of the kidneys and may be overlooked on superficial examination (Fig. 10). On section, the cortex and medulla are not clearly demarcated from each other, and both are honeycombed by innumerable small cysts with a resultant spongy appearance of the renal parenchyma. The renal pelvis and calyces are distorted, not by isolated cysts, but by the increased bulk of the surrounding tissue (Fig. 11).

Histologically there is usually some increase of connective tissue, especially in the medulla[37]; the cortical cysts, on the contrary, are closely approximated or are separated by only small amounts

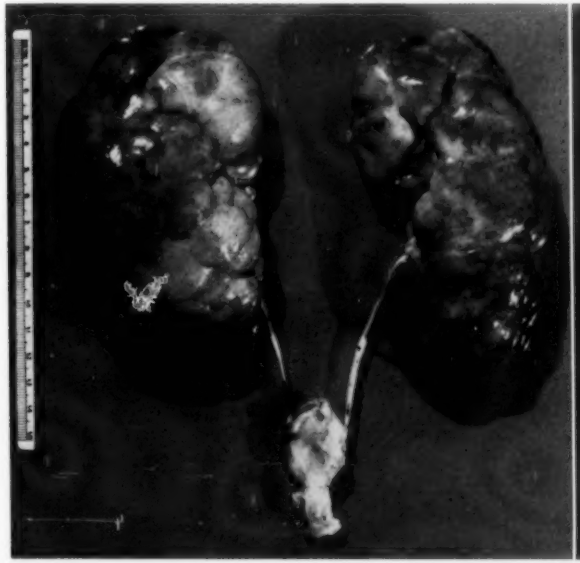

Fig. 10.

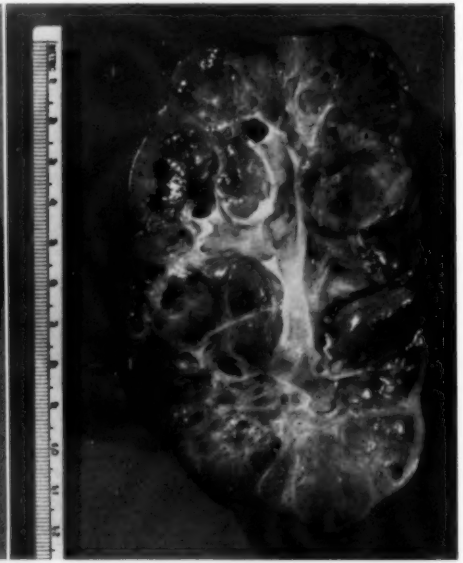

Fig. 11.

Fig. 10.—Polycystic disease of the kidneys in an infant 9 months of age. Note the normal shape of the enlarged kidneys. The cysts are not readily apparent on the external surface.

Fig. 11.—Cut surface of one of the kidneys depicted in Fig. 10. Note the elongated renal pelvis and the spongy appearance of the parenchyma.

of connective tissue (Fig. 12). The presence of large amounts of fibrous tissue in the cortex tends to militate against a diagnosis of true polycystic disease and favors a diagnosis of renal hypoplasia. Potter[22] divides polycystic kidneys into two major groups, those in which the amount of renal connective tissue is normal and those

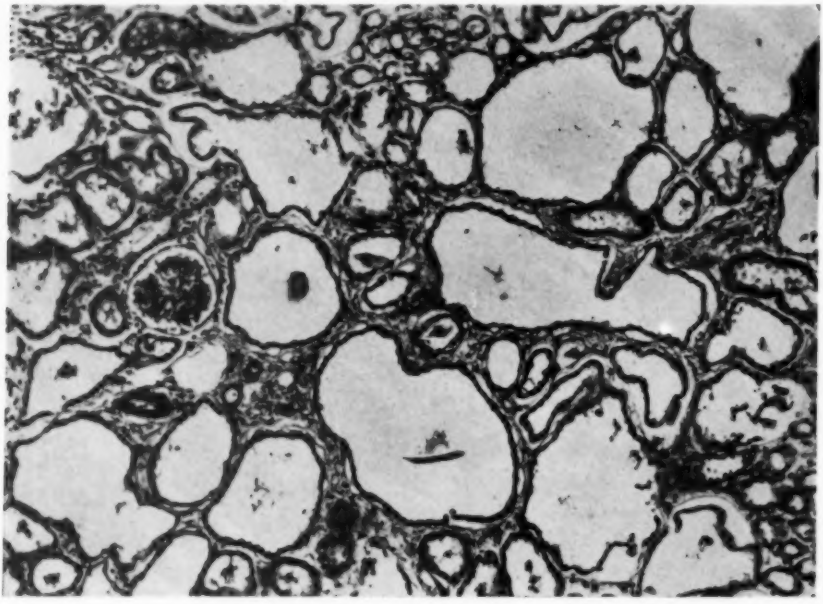

Fig. 12.—Photomicrograph of the polycystic kidneys shown in Figs. 10 and 11. Note the absence of any significant increase of connective tissue in the cortex in contrast with the appearance of hypoplastic kidneys.

in which it is increased. According to the present classification, only the former would be considered as polycystic kidneys; those with large amounts of connective tissue, especially in the cortex, would be considered as hypoplastic and not as true polycystic kidneys. Islands of hyaline cartilage may be observed in true polycystic kidneys[37] but are far more frequent in hypoplastic kidneys. The cysts, which for the most part are lined by cuboidal epithelium, may be glomerular or tubular in origin and many appear to represent simple elongation and dilatation of tubules. With few exceptions, the cysts do not communicate with the renal pelvis.

Other anomalies are frequently present in association with polycystic disease of the kidneys in infants[38]; these include polydactylism, hydrocephalus, and clubfeet. Genitourinary anomalies may be present, but in certain instances in which these have been described the kidneys would not be included in the present category of true polycystic disease.[39-41] Polycystic disease of the liver is probably considerably more frequent in infants with true polycystic kidneys than would be indicated by figures based primarily on the disease in adults. Rall and

Odel[38] found that 15 of 46 patients (33 per cent) with polycystic disease of the kidneys also had polycystic livers, but their patients were principally adults. Cysts in other viscera, e.g., the pancreas or even the lungs, are less frequently observed.

Admittedly, certain features suggest that such a differentiation of hypoplastic kidneys from true polycystic disease of the kidneys is not a valid one. For example, polycystic disease of the liver may be associated with hypoplastic kidneys containing cysts; although such an association is less frequent than in true polycystic disease of the kidneys, it certainly suggests that polycystic and hypoplastic kidneys are not sharply separable. Nevertheless, clinical, pathologic, and hereditary features of the two diseases appear to be sufficiently distinctive to justify their differentiation. Only by adhering to rigid diagnostic criteria can more information concerning the exact nature of each of them be gained.

The clinical manifestations of polycystic disease of the kidneys in infants vary according to the severity of the process. In the most severe types death occurs in utero or very shortly after delivery. Massive abdominal enlargement results from the bulky renal masses and may be further enhanced by ascites and hepatomegaly. The facies may suggest that associated with bilateral renal agenesis. In infants who survive for longer periods of time, the clinical manifestations are those of chronic renal insufficiency with vomiting, failure to gain weight, anemia, acidosis, slight albuminuria, azotemia, and the presence of bilateral palpable abdominal masses. Severe hypertension may be present even in the first few months of life, in association with cardiomegaly and signs of congestive cardiac failure.[42] In those patients with long standing chronic renal insufficiency, dwarfism with secondary hyperparathyroidism and renal rickets may result. Although the classical "spider" pelvis with stretching, elongation, and narrowing of the pelvis and calyces may be observed,[43] distortion of the collecting system may be minimal or absent. Persistent nephrograms may be observed in some infants after the intravenous injection of contrast medium and, in the absence of evidence of obstruction of the urinary tract, may be of diagnostic value. Mottled and linear radiolucent defects in the nephrographic density are said to be pathognomonic of polycystic disease of the kidneys.[44]

The pathogenesis of polycystic disease of the kidneys is unknown. The neoplastic and inflammatory theories of origin are no longer acceptable. Cystic dilatation occurring as a result of failure of union of the collecting ducts with the metanephric blastema is untenable as a theory of origin, since the metanephric blastema does not differentiate in the absence of contact with the ureteral bud or its branches.[45] Moreover, in polycystic disease the point of atresia of the nephron usually does not correspond to the point of junction of the nephron with the collecting duct. Kampmeier[46, 47] attributed the cysts to a persistence of cystic nephrons which normally occur for a short time as a degenerative change in the first few generations of metanephric derivatives. Such a theory might explain the occurrence of cysts in the peripelvic region but hardly accounts for the widely scattered and

more peripherally located cysts. An overgrowth of tubules, occurring as a hamartomatous malformation or "hamartiosis," dependent upon defective action of embryonic organizers as a result of an inherent abnormality of the germ plasm, has been suggested as giving origin to both polycystic kidneys and polycystic liver.[48] Although proof of this theory is not available, the histologic appearance of the polycystic liver in infants is certainly that of an overgrowth of bile ducts and often of connective tissue; this is, however, not as apparent in polycystic kidneys. Norris and Herman[49] attribute polycystic kidneys to a defect of the germ plasm which manifests itself only after the development of the kidneys during embryonic life has progressed normally for a considerable period of time. Focal cystic dilatations of nephrons and of collecting ducts are followed by isolation, segmentation, and the development of multiple cysts. These changes resemble the degenerative process which occurs normally in the mesonephros and in the early generations of the metanephros. The cysts are thus attributed to an extension of this normal degenerative process, so as to involve not only the first but also later generations of metanephric tubules.

Although polycystic kidneys have been reported in all age groups, relatively few deaths from the disease occur between infancy and adult life. Since both the infantile and adult forms of the disease are believed to be congenital in origin, it is difficult to explain this gap in the age at onset of clinical manifestations. It may be assumed that the infants who die have a severe form, whereas patients with milder forms survive into adult life, the cysts growing slowly or not at all during childhood. Such an explanation, however, is not entirely satisfactory, and certain authors have suggested that infantile and adult forms of polycystic disease represent two independent disease entities.[26, 50, 51] Thus, reconstructions of polycystic kidneys have revealed that the tubular cysts are usually connected with the excretory ducts and renal pelvis in adults, but not in infants. Glomerular cysts, however, do not communicate with the remainder of the nephron in either infants or adults.[52] Moreover, the cystic nephrons of the adult retain a considerable part of their functional activity and presumably play a role in the formation of urine, whereas this is less frequently true of the cystic nephrons in infantile polycystic disease.[53] These observations, although admittedly limited in infants, suggest that morphologic and resultant functional differences exist between the infantile and adult forms of polycystic disease; these differences would explain the early death of infants with the disease and the delayed onset of clinical manifestations in adults, in whom the cystic nephrons contribute at least in part to the formation of urine.

The hereditary pattern of polycystic disease of the kidneys also suggests a difference between the infantile and adult forms of the disease. The occurrence of siblings with infantile polycystic kidneys is well recognized,[54] and the occurrence of adult types of polycystic kidneys in multiple generations as well as in siblings has been reported in a number of families.[23, 50] However, no definite reports of adults with polycystic disease giving birth to

offspring who die as a result of infantile polycystic kidneys are available[50, 51]; such an association might be expected if the two types merely represented different degrees of severity of the same disease process. Instead, the genetic pattern in the adult type is that of a mendelian dominant, while in the infantile form it is more suggestive of a recessive characteristic.

It must be admitted, however, that objections may be raised to all of the considerations which would tend to separate infantile and adult forms of polycystic disease as independent disease entities. The macroscopic appearance of the two is often quite different, with the cysts being of relatively uniform size in the infant and of extremely variable size in the adult. This difference, however, might well merely reflect differences in the duration of the process. Tubular cysts in infants in general do not communicate with the renal pelvis, whereas in adults they do, and the associated functional differences between the cysts in infants and in adults may only reflect different degrees of severity of an essentially similar process. Even the variations in the hereditary pattern of the two diseases do not offer irrefutable proof of their independent nature, since when a hereditary disease occurs in several forms, that form caused by a dominant gene will usually have a later age of onset than will the form caused by a recessive gene.[50]

The more frequent association of other congenital anomalies with the infantile than with the adult form of polycystic disease cannot be considered as indicative of any fundamental difference in the two disease processes. The occurrence of polycystic disease in other viscera than the kidneys in both infants and in adults with polycystic kidneys actually suggests an identity of the two forms of the disease.

It is apparent, then, that dogmatic statements concerning fundamental differences between infantile and adult forms of polycystic disease are not warranted at the present time. The evidence rather strongly suggests that they represent two distinct disease processes, but proof of this can be established only by careful study of many more patients, in whom rigid diagnostic criteria must be maintained.

Medullary Cysts.—Finally, there remains a small group of patients in whom numerous cysts are found which produce a honeycomb-like pattern in the renal medulla, with few or no cysts in the cortex.[55, 56] The clinical manifestations are those of prolonged severe anemia associated with azotemia and in some instances with hyperphosphatemia, hypocalcemia, and hypertension. The kidneys are small or of normal size and contain numerous cysts which are predominantly medullary in location. As a rule there is no significant increase of connective tissue about the cysts, but varying degrees of glomerular fibrosis and tubular atrophy may be present in the renal cortex. There may be associated cysts of the liver or pancreas. The majority of the patients have been young adults. The true nature of these lesions is not clear, and it is quite possible that they should not be classified as examples of true polycystic disease.

SUMMARY

Simple renal cysts, perinephric cysts, and multilocular cysts of the kidney

are rare in infants and children. They manifest themselves by the presence of an abdominal mass which may be interpreted clinically as a Wilms's tumor.

The clinical, pathologic, and hereditary features of true polycystic disease of the kidney appear to be distinct from those of renal hypoplasia, and every attempt should be made to differentiate these two diseases. The cystic kidneys which may be associated with intrauterine urethral obstruction may represent instances of renal hypoplasia and should not be interpreted as true polycystic disease of the kidneys. Similarly, the unilateral multicystic kidney, which manifests itself by the presence of an abdominal mass, is a form of renal hypoplasia and does not represent unilateral polycystic disease of the kidneys.

There is evidence to indicate that infantile and adult forms of true polycystic disease of the kidneys represent two independent entities. Further study is necessary before this fact can be established unequivocably.

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INCONTINENTIA PIGMENTI

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IN THE differential diagnosis between various types of vesicular skin lesions in infants during the neonatal period, a large number of diseases have to be considered, notably, congenital syphilis, various forms of epidermolysis bullosa, pemphigus neonatorum, contact dermatitis, and dermatitis herpetiformis. If all of these diagnoses are ruled out, and also the familiar virus diseases associated with vesicles (herpes simplex, Kaposi's disease, chickenpox, or smallpox), the physician will be confronted with a problem. It may then be advisable to bear in mind incontinentia pigmenti, which probably is not altogether uncommon and is easily recognized once a case has been studied.

Incontinentia pigmenti was described in 1925 by Bardach, who reported, under the name of *systematisierte Naevusbildungen,* the typical symptomatology in a pair of monozygotic twins. In the same year Bloch reported a case in a 2-year-old girl with pigment anomalies which he characterized as incontinentia pigmenti. The disease has since been known by that name, although attempts have been made to introduce other designations.

In 1927, Sulzberger[20] reported Bloch's case in greater detail, but since Bloch was then considered to have priority and Sulzberger had described the morbid anatomy exhaustively, the disease has since been most commonly known as the Bloch-Sulzberger syndrome. Lechleuthner, in 1925, and Siemens (same case in 1929) have also been credited with priority for the disease, which the latter author called melanosis corii degenerativa. In the opinion of Epstein and co-workers, who described a bullous variation of the condition, Bardach has priority. Carney,[4] 1951, in an excellent and concise paper, called attention to the early vesicular stage. Carol and Bour, 1941, felt that the disease was best characterized by the name of melanoblastosis cutis linearis or systematisata.

In recent years, papers on the subject, generally comprising only a few cases, have been reported from several countries in and outside Europe.[2-4, 6-10, 14, 16-22] In the Scandinavian literature, up till 1957, some cases have been reported,[1, 11-13] all from Denmark. Jensen[13] described a case with pronounced ocular lesions and positive serum reactions for toxoplasmosis. In 1958 two papers were published in Sweden[17, 18]; one described the same cases as in this paper, the other paper dealt with a new case.

One of the most interesting features of this disease is that the skin lesions, which appear in early infancy, merely usher in the condition and are only

This investigation was conducted with the aid of grants from the Östergötland County Council.

a part of the symptomatology as a whole. Incontinentia pigmenti is regarded as an ecto- and mesodermal polydysplasia with early manifestations consisting of bullous and vesicular cutaneous lesions in the neonatal period and infancy, gradually changing to verrucous and, eventually, to pigmented skin lesions that fade with the years. In most cases there are concomitant neurologic symptoms, e.g., convulsions, central motor disturbances, sometimes oligophrenia, and, often, varying ophthalmologic symptoms. In at least two cases, enucleation had been resorted to on the suspicion of glioma. Very typical of the disease are deep-going anomalies of the dentition, frequently in the form of delayed eruption with pointed hypoplastic, widely spaced teeth. Occasionally, as in our first case, there are dentitional disturbances so grave as to warrant the designation of hypodontia or partial anodontia. The great majority of cases occur in girls (there are only 4 males among 80 reported cases), and the disease is considered to be (predominantly?) hereditary. Different symptoms may be manifest in different generations, which makes it difficult to verify the heredity.

Since pediatricians are showing mounting interest in congenital anomalies and genetics, it seems worth while reporting three cases studied in recent years at the Children's Hospital, Linköping. Two of the patients have been observed at the pediatric department through the various stages up to abating pigmentation, though one of them for only one year. The third patient was first observed at that department when she was 2 years old.

CASE REPORTS

CASE 1.—P. H. F., a boy, was born on Sept. 10, 1953. Parturition was normal, and the weight at birth was 3,790 grams. A second child, a sister, is healthy.

Heredity.—The 56-year-old maternal uncle of the mother is a chondrodystrofic dwarf. His length is 134 centimeters and he is of normal intelligence. There are no anomalies of the eyes or the skin. All the teeth have been lost. The father had progenia, had lost his upper teeth early, and suffered from acne rosacea. The parents were not related.

Fig. 1.—CASE 1, The vesicular stage, changing to the verrucous stage, 1953.

Skin.—There had been numerous vesicles and "pustules" on the body and face at birth; eventually, a linear arrangement of papules and vesicles appeared, chiefly on the dorsal surfaces of the legs and buttocks (Fig. 1) and on the back. These lesions finally changed, via a verrucous stage, to hyperpigmentation that persisted locally, but decreased in intensity, and

invariably showed a distinct linear tendency. On examination in 1957, at the age of 4 years, there was "café-au-lait" pigmentation in long, fairly pale streaks on the extremities, notably the back of the legs, and more conspicuously on the trunk in the form of regular arciform and horizontal streaks about 1 cm. wide, which appeared to coincide with the segmental innervation (Fig. 2). On the back, the pigmentation sometimes cross the midline, but on the abdomen it ceased a few centimeters therefrom. There were a few discrete patches on the face. Comparison of photographs from 1953 (Fig. 2) and 1957 (Fig. 3) showed that the pigmented areas had diminished in extent. It was characteristic that some of these hyperpigmented sites became reddened and verrucous at times of gastrointestinal infections. There were isolated verrucous areas on the feet (Fig. 4).

Hair.—Alopecia areata with hyperpigmentation.

Teeth.—Delayed and very defective dentition. At the age of 1½ years, the patient had only 3 teeth, which were hypoplastic and pointed. At the age of 4 years the child had only 5 upper and 5 lower teeth, of which 3 upper and 4 lower were pointed and widely spaced (Fig. 5). Radiograms disclosed only 12 dental germs. The patient suffered a grave case of hypodontia (partial anodontia).

Fig. 2.

Fig. 3.

Fig. 2.—Case 1, The pigmented stage, 1954 (compare with Fig. 3, 1957).
Fig. 3.—Case 1, The pigmented stage, 1957.

Neurologic Findings.—The patient had convulsions in the neonatal period. Lumbar puncture showed no appreciable disease. The Wassermann reaction was negative. On examination, at age 4 years, some bradylalia and mental peculiarities (lack of spontaneity) were discovered. Babinski's test was possibly positive on the left side.

The electroencephalogram was normal in 1957.

Ophthalmologic Findings.—(1957) Eyelid skin was thin, wrinkled, and atrophic. Media and eye grounds showed no appreciable disease. There were no angioid streaks. Antisometropia was present. There had been earlier periodic concomitant strabismus sursum vergens, but this had subsided. Right eye was +0.5 diopters and had full visual acuity. The left eye was −4 diopters and had impaired vision; this eye will probably be amblyopic.

cranium and the skeleton showed nothing pathologic. The electrocardiogram was normal. Dye test (Sabin-Feldman) and the complement fixation test were negative for toxoplasmosis.

Histopathologic Findings.—(These examinations were performed by Dr. Fredrik Wahlgren, Senior Pathologist at the Pathology Department of Södersjukhuset, Stockholm.) In the vesicular stage, epidermis showed some acanthosis, slight discrete hyperkeratosis, and edematous opening-out. Eosinophilic leukocytes were present here and there. In a few places, superficial vesicles approximately at the level of the keratohyaline layers were found (i.e., not coinciding with localization in the dermatitis herpetiformis) (Fig. 6). Corium connective tissue was edematous. In papillary and subpapillary layers were fairly abundant, diffuse accumulations of inflammatory cells, largely eosinophilic leukocytes.

Fig. 4.

Fig. 5.

Fig. 4.—Case 1, Verrucous areas on the feet in 1954.
Fig. 5.—Case 1, The pathologic dentition, 1957.

Other Findings.—The patient's course was afebrile. The sedimentation rate was low. The weight increase was satisfactory. The blood examination was as follows: Coincident with the early vesicular lesions there was conspicuous eosinophilia (maximum 34 per cent in peripheral blood); otherwise, nothing was pathologic. (Eosinophilia was also present in the affected areas of skin.) All bacteriologic cultures from the vesicles were negative. Cultivation for viruses was not done. Radiograms of the

In the pigmented stage (Fig. 7) the epidermis was slightly thickened and edematous in patches. At these sites, the corium showed increased numbers

Fig. 6.

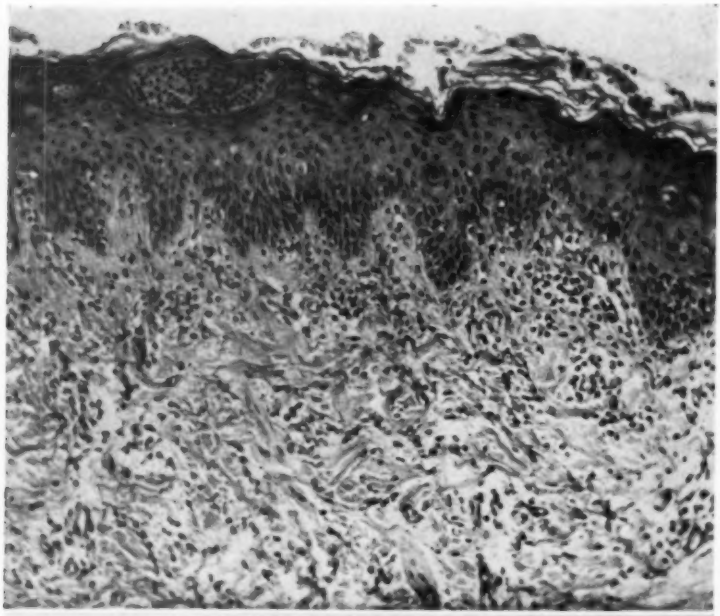

Fig. 7.

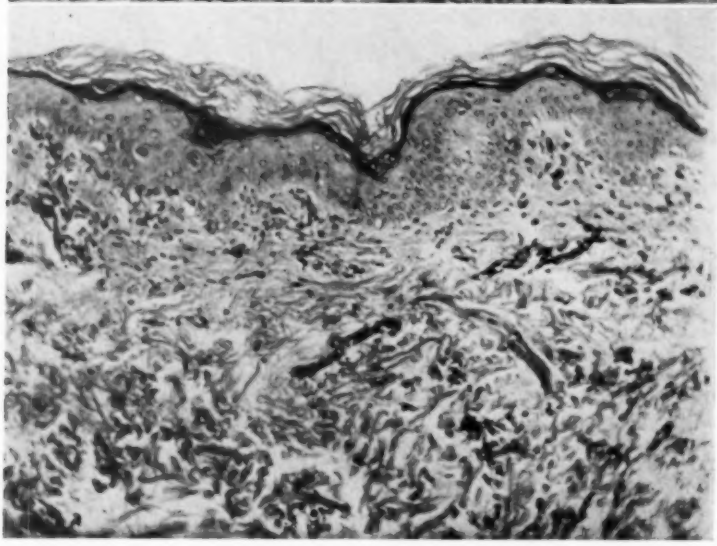

Fig. 6.—CASE 1. A photomicrograph in the vesicular stage, 1953, showing vesiculation with eosinophil cells superficially in the epidermis.

Fig. 7.—CASE 1. A photomicrograph in the pigmented stage, 1957, showing an increased number of chromatophores and clumps of melanin in the corium.

of chromatophores and clumps of melanin pigment. The findings were probably typical of incontinentia pigmenti.

Tentative Therapy.—(Vesicular stage) Aureomycin had no effect; sulfonamide had some influence on the eosinophilia but no definite effect on the vesiculation. Cortisone produced a marked reduction of the eosinophil count; from 7,350 to 1,000 per cubic millimeter, without demonstrably influencing the disease in other respects. The condition showed a spontaneous tendency to improve, which made evaluation of therapy difficult.

CASE 2.—A. K. L., a girl, was born on Oct. 10, 1956. The patient is an only child. The pregnancy and parturition were normal. Weight at birth was 3,500 grams.

Heredity.—Nothing typical of incontinentia pigmenti was known. The parents were not related.

Skin.—Some vesicles had been observed on the left upper arm at birth, and in the next few days they spread over large areas of the body. Eventually, there was the typical linear arrangement of yellowish-red maculopapules and vesicles on the dorsal surfaces of the thighs and buttocks as well as some verrucous lesions; there was also involvement of the trunk and face. The infant's general condition was excellent; the child gained weight and was afebrile. The sedimentation rate was normal. Cultures from the vesicular fluid proved negative. Cultivation for viruses was not done. Jodine test for dermatitis herpetiformis was negative. After a month or so, there were verrucous and infiltrated areas in long streaks on the back of the legs and buttocks (Fig. 8) and across the trunk (Fig. 9). There was incipient pigmentation. Infiltrations later abated, leaving a grayish-brown pigmentation. At the ages of 6 months and 1 year, respectively, pigmentation was distinctly paler (compare Figs. 9 and 10). Infant was then adipose.

Hair.—The hair was fairly thin, but no alopecia was present.

Teeth.—There were no teeth at the age of 6 months and three at the age of 1 year, one of which seemed to be pointed. Normal dentition in 1958.

Neurologic Examination.—Nothing pathologic was observed at the age of 1 year. The patient was well developed with respect to age.

Ophthalmologic Findings.—Some paleness of the papillae was observed at the ages of 1 month and 6 months; an abnormally marked lens border was noted at age 1 year.

Laboratory Tests.—Eosinophilia was 23 per cent in acute stage. The Wassermann reaction was negative. Anemia was present during the first 3 months with a hemoglobin of approximately 8 Gm. per cent and a red blood cell count of 3 million per cubic millimeter; after that anemia was slight.

Histopathologic Findings.—(The examinations were performed by Dr. Fredrik Wahlgren.) In the vesicular stage, the epidermis was thickened in some places, with edema and infiltration of eosinophilic leukocytes. Corium at these sites was edematous and infiltrated with inflammatory cells, largely eosinophils. There was no fully typical vesiculation. Deeper parts of the corium were more or less normal. The lesions appeared to be most consistent with dermatitis herpetiformis. Diagnosis of incontinentia pigmenti was established later. (The parents have so far refused to permit biopsy of pigmented area.)

Tentative Therapy.—In the vesicular stage, sulfapyridine resulted in elevation of temperature and disappearance of all eosinophils from the blood. Further attempts with the same drug had similar results. The vesicles were unchanged.

CASE 3.—Å. J., a girl, was born on Sept. 19, 1953. Pregnancy and parturition were normal. Weight at birth was 3,750 grams. The patient was the third of four children.

Heredity.—Father had had brown pigmented areas round the trunk "following chickenpox" (?). A maternal

Fig. 8.

Fig. 9.

Fig. 10.

Fig. 8.—Case 2. The vesicular stage, changing to the verrucous stage (age 2 months, December 1957).

Fig. 9.—Case 2, Vesicular stage, changing to the verrucous stage (age 2 months, December 1957).

Fig. 10.—Case 2. The pigmented stage, 1957.

aunt had had a vesicular eruption affecting the whole right side of the body at the age of 1 month; there was no residual pigmentation. The mother and another of her sisters had anisometropia and myopia. One brother had a harelip. The parents were not related.

old. The diagnosis was pyodermia and gastroenteritis. She was readmitted between the ages of 2 and 3 months, and at age 5 months, with the diagnosis hereditary epidermolysis bullosa being given. On the last occasion she had intertriginous erythema below the chin.

Fig. 11.

Fig. 12.

Fig. 11.—CASE 3, The pigmented stage (age 4 years, 1957).
Fig. 12.—CASE 3, The pigmented stage (age 4 years, 1957).

Skin.—Ten hours after birth a few pea-sized vesicles were observed on the inner surface of the right forearm. Further vesicles developed in the next few days and eventually covered the abdomen, arms, face, especially above the eyebrows, ears, and neck; however, only a few were present on the cheeks. There were vesicles in long streaks down the back of the legs and on the feet. The patient was transferred to a children's hospital and kept there from the age of 2 weeks until 4 weeks

The gluteal skin was reddened and infiltrated. On the arms, especially inside of the forearms, and on the dorsal surfaces of legs were moderate numbers of pale red, fairly hard, and infiltrated maculopapules without vesiculation. On the trunk and extremities were areas of gray pigmentation coinciding with the earlier sites of vesiculation. The facial vesicles had subsided without residual pigmentation. Vesicles on the scalp had left a hairless pigmented patch in one place.

On the hands, notably the dorsal surface of the right thumb and middle finger, were a few fresh, severely erythematous efflorescenses with dried vesicles. General condition was good and increase of weight was normal.

The pigmented areas increased in intensity up to the age of 1 to 1½ years; then they gradually faded, although they were probably unchanged in extent, and possibly disappeared in some places. When examined in 1955, in the Dermatology Department, Linköping Hospital, at the age of 2 years, the patient had extensive grayish-brown pigmented areas on trunk, groin, and axillae, forming a reticular and linear pattern. The lines crossed the trunk diagonally and ran down the dorsal surfaces of the legs. During febrile upper respiratory infections, the pigmented areas became reddened, elevated, pruritic, and, in some places, discharged fluid. The pale skin between these areas was quite normal. On examination at a children's hospital, in 1957, the patient's condition was more or less unchanged (Figs. 11 and 12). She was well developed for her age, but her speech was somewhat retarded and unclear, although there was no bradylalia. There was a mild, dry eczematous lesion on the right dorsum pedis. In summer of 1957, she had shown, at that site, fresh formation of clear coffee-bean-sized vesicles. Abdominal skin was somewhat rough and dry with occasional scratch marks, mostly in the pigmented areas. A few verrucous excrescences were observed on fingers and toes.

Hair.—There was alopecia areata with hyperpigmentation at the site of vesiculation during infancy.

Teeth.—

Clinical examination: The child had normally developed milk teeth except the upper lateral incisors, the crowns of which were abnormally slender and pointed. Only the left lower first premolar was carious. Gingiva and mucous membranes were normal.

Radiographic examination: Dental germs of right upper lateral incisor and left upper second premolar were absent; that of the left upper lateral incisor resembled a small bell. The right upper second premolar had a germ of normal size, but not normal radiographic contrast. Dental germs of lower second premolars were absent; that of right lower first premolar appeared as a small bell. The examiner (Dr. B. O. Wiklund) made a reservation for undetected details. The calcification was incomplete.

Neurologic Findings.—Possibly, there was some speech retardation. At the age of 4 years, the speech was very unclear. There was no spasticity or convulsions.

Ophthalmologic Findings.—Strabismus convergence of the left eye was present. In the right eye, visual acuity was 6/5 ±0 diopters. The left eye was unable to fix and was +8 diopters. The patient had amblyopia ex anopsia and anisometropia. The media were normal. No anomalies of pigmentation were demonstrable in eye grounds (Scherling).

Laboratory Findings.—During vesicular period in infancy, the maximum peripheral eosinophilia was 30 per cent. The Wassermann reaction, the Kahn, and the Meinicke tests were negative. Cultivation of vesicular fluid showed growth of *Staphylococcus aureus* (probably a contamination). Virus cultivation was not done. In the pigmented stage (1957) the eosinophilia count was 7 per cent. Blood values were otherwise in normal range.

Histopathologic Findings.—(Examination by Dr. Wahlgren.) In the pigmented stage, epidermis in the biopsied area was slightly thickened and edematous, but otherwise showed no changes. In superficial layers of the corium, at a few sites, were clumps of melanin-pigmented chromatophores. There was no inflammatory cell infiltration. The picture resembled, in principle, that earlier observed in cases of incontinentia pigmenti.

DISCUSSION

For the differential diagnosis of vesicular skin lesions in infants, there is an excellent scheme in a paper written by Lewis and his colleagues,[15, 23] although it does not include incontinentia pigmenti. Of the diseases mentioned in the introduction, notably epidermolysis bullosa and various forms of pyodermia have to be considered. The vesicles in epidermolysis bullosa are much thinner and more widespread than those associated with incontinentia pigmenti. They rupture and discharge a more or less copious, thin secretion. They are frequently localized to areas exposed to pressure. The small vesicles in incontinentia pigmenti, often no bigger than lentils, are surprisingly resistant to compression and palpation. They sometimes appear to have thick contents, which occasionally seem so yellow, through the vesicular wall, as to be suggestive of xanthomatosis. Moreover, they are often concomitant with firmer papular areas and, in many cases, incipient verrucous formations among the vesicles. The linear arrangement in incontinentia pigmenti is absent in epidermolysis bullosa. The physician who has observed a few cases of epidermolysis bullosa and one or two of incontinentia pigmenti will not be likely to confuse the two conditions. Presumably, it is more difficult to distinguish incontinentia pigmenti from dermatitis herpetiformis, which, in fact, is the condition most frequently diagnosed in obscure cases that have later proved to be incontinentia pigmenti. Indeed, it long remained the diagnosis in the first of our cases. Personally, I have not observed dermatitis herpetiformis in children and, therefore, have nothing to add to data in the literature. From the latter it is evident, however, that even infantile dermatitis herpetiformis is associated with groups of vesicles and not long streaks as in incontinentia pigmenti, sometimes with urticarial formations as well. In adults the itching is intense, but in the newborn infant it is not a distressing symptom, so that its absence perhaps cannot be accounted any major importance. Histopathologically, it may be possible to distinguish between the vesiculation in incontinentia pigmenti and that in dermatitis herpetiformis, the vesicles being more superficial in the former disease (CASE 1).

In regard to the differential diagnosis relative to pyodermia, bacterial cultivation will doubtless be decisive, also the afebrile and benign course irrespective of antibiotics, and the absence of contagiousness.

In the light of these three cases, a few special considerations are worth discussing. The first case is, in all respects, quite characteristic of incontinentia pigmenti; the only unusual feature is that it occurred in a male infant. The disease, as mentioned above, is very rare in males, and the question whether this was actually incontinentia pigmenti might be debatable. Franceschetti and Jadassohn[8] discussed the possibility of two different types of pigment anomalies, both of which might have been incorrectly referred to the Bloch-Sulzberger syndrome. The present male case might then, conceivably, be assignable to the Naegeli form of the disease, which is equally common in the two sexes. If this were so, however, the boy would not normally have shown neurologic symptoms (notably ocular),

nor the delayed dentition and the anodontia but, rather, yellow-spotted teeth and sensitivity to heat due to the inability to sweat. Nothing of the kind was observed in this case, although the child was not subjected to a test with pilocarpine. Moreover, the pigmentation should be *reticulée* in the Naegeli form, and judging by illustrations in the relevant paper the present case does not conform thereto, either in color or type. It is closely consistent, however, with *pigmentation en éclaboussures* as in the Bloch-Sulzberger syndrome. I have therefore ventured to assume that this is the fifth male case of incontinentia pigmenti (Bloch-Sulzberger syndrome). (The diagnosis was verified by Sulzberger, among others, at the International Dermatology Congress in August, 1957.)

In CASE 2, which related to a girl, no comments are required regarding the correct diagnosis. True, some of the common neurologic and ocular symptoms were absent here, but the patient is still quite young and, moreover, these organic changes are reported to occur only in just over one-half of the cases.

In CASE 3, also a girl, the diagnosis must be regarded as established following the demonstration of both a vesicular initial stage and typical linear pigmented areas, ocular lesions, partial hypodontia, and typical histopathologic findings in pigmented areas of the skin. Worthy of note is that the hypodontia was not manifested until the dental germs had been examined radiologically.

Many investigators consider the term incontinentia pigmenti to be a misnomer. It originated from the assumption that the basal layer of the epidermis was "incontinent" and allowed melanin to penetrate to the corium, where it was dealt with by connective-tissue cells, or chromatophores. This view has recently been strongly criticized.[21] It is pointed out that no migration of pigment has ever been observed, and the pigment granules in the basal epidermal layer and in the corium vary in size, so that the corium probably has its own pigment production. Also, there is not necessarily any lack of pigment in the basal layers above the pigment-rich parts of the corium, as might be expected if pigment migration occurred. Undeutsch and associates[21] have excellent illustrations showing all variations that may occur in this respect; this also tends to disprove the theory of incontinence in the basal layer. Some other designation for the disease, as for instance, melanosis corii degenerativa (Siemens), therefore seems preferable, but the term incontinentia pigmenti has become so familiar that it is considered best to retain it.

The cause of the conspicuous linear arrangement of the pigmented areas on the trunk in, e.g., the present CASE 1, and also that on the dorsal surfaces of the legs and buttocks, is not known with assurance; but certain observations[22] are suggestive of imperfectly developed sensory nerve fibers with absence of overlapping in the exudative and subsequently pigmented areas. These zones should accordingly be more susceptible than others to varying stimuli, to which they respond with skin lesions of the type outlined above. In the course of time, it is thought, vasomotor fibers then develop and, after a few months, cause the exudation to subside in the infant and the pigmentation to remain. Also

possible is that the basal layers in these susceptible zones are easily injured, giving rise to abnormal pigmentation which instead appears in the corium, resulting in the bizarre pigmented areas. These theories are possibly consonant with the observations on the hereditary factor in the disease. But it is far more difficult to reconcile the heredity with those virus theories that have been propounded by some authors. Grüneberg,[9] for instance, has subscribed to a theory of intrauterine virus infection as the etiology of the disease. Yet repeated attempts to cultivate viruses from vesicular fluid have invariably failed.* Probably, we are concerned here, rather, with a hereditary ecto- and mesodermal polydysplasia, as most investigators now believe. The relationship to toxoplasmosis should be studied in more detail by serologic examinations of old and new cases.[13] In the first of the present cases, serologic tests for toxoplasmosis were quite negative. Since the other two patients had no ocular lesions, toxoplasmosis was considered unlikely.

It is useful to know of the disease when seeking to elucidate the cause of vesicular skin lesions in infants, and when investigating skin diseases and alopecia associated with pigmentation. Incontinentia pigmenti should also be borne in mind in the evaluation and classification of children with central motor disturbances, with or without oligophrenia, and when examining cases with ocular and dental anomalies.

SUMMARY

Three cases of incontinentia pigmenti are reported, one of them in a boy 4 years of age. (In males the disease is extremely rare. Not more than four of the 80 cases published since 1925 have been males.) The other two cases were in girls of 1 and 4 years, respectively. Two of the cases were observed in all three stages: the vesicular, the verrucous, and the pigmented. The older child's condition was also observed in the fourth stage: the fading pigment stage. The histopathologic findings were typical for the disease, and there was blood eosinophilia in the acute early stage. The boy had various neurologic manifestations, such as convulsions in the neonatal period; strabismus and anisometropia with myopia and unilateral impaired vision; bradylalia; alopecia areata with hyperpigmentation; late eruption of defective teeth, and partial anodontia in the permanent dentition.

No relationship to toxoplasmosis was found.

The second case, a girl of 1 year, had typical skin changes at various ages, but no real neurologic or ophthalmologic changes.

The third case, a girl of 4 years, was studied at another hospital in the early stages and transferred here in the pigmented stage. She showed, in addition to the extensive pigmentation, partial hypodontia of the permanent teeth, strabismus with amblyopia ex anopsia, anisometropia, and alopecia areata with hyperpigmentation.

The etiology is discussed, and the probability stressed that incontinentia pigmenti is referable to the ecto- mesodermal polydysplastic diseases, mostly affecting the female sex.

*Personal communication.

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A CLINICAL STUDY OF AN EXANTHEM DUE TO ECHO VIRUS TYPE 9

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WITHIN the past five years two infectious exanthems have been etiologically related to enteric cytopathogenic human orphan viruses (ECHO).[1] Neva[2-6] first described the Boston Exanthem in 1954, and subsequently defined a similar outbreak in Pittsburgh in 1956. Continued investigation has revealed that the causative agent is ECHO virus type 16.[7]

Rash and aseptic meningitis due to ECHO virus type 9 have been described since 1953, in Australia,[8] England,[9, 10] Belgium,[11-13] Canada,[14] and the United States.[15, 16] The rash occurred in but 13 to 50 per cent of the cases. In one report from England only rash, headache, and fever without meningismus were described.[17] Kleinmann and associates[15] observed many cases of exanthem alone in their survey of ECHO 9 virus infection in Minnesota during the summer of 1957.

It was the observation of the first three cases of exanthem described below and the curiosity thus aroused that initiated the virologic investigation and epidemiologic survey of the Minnesota epidemic. All of these thirteen cases of "new measles" had been seen before the first case of aseptic meningitis was brought to our attention. As our study progressed, it became obvious that the same viral agent was responsible for cases of exanthem alone, aseptic meningitis alone, aseptic meningitis plus exanthem, and "summer grippe."

As mentioned above, the aseptic meningitis syndrome was well known, but documented cases of ECHO 9 viral rash alone were extremely few. Our interest was in the unveiling of a new "measles," the clinical and laboratory observations of which are presented below.

METHODS OF INVESTIGATION

Throat swabs, fecal specimens, and acute- and convalescent-phase sera were obtained from almost all subjects who presented this unusual exanthem. As a detailed virologic investigation of this entity is the basis for a separate report,[18] only a brief description of the laboratory techniques will follow.

Throat swabs were immersed in nutrient broth immediately after collection. After centrifugation of the broth, the supernatant fluid was decanted, antibiotics were added, and aliquots ampuled for storage at –70° C. Stool specimens were initially frozen at –70° C. and later suspended in distilled water. Then, as above, after centrifugation, antibiotics were added and the specimens ampuled for storage at –70° C. Acute- and convalescent-phase sera were stored at –20° C.

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Cell cultures of monkey (cynomolgus and rhesus) kidney, HeLa, human amnion, and human foreskin were inoculated with undiluted specimen material and maintained at 37° C. These preparations were observed for 10 to 21 days for evidence of cytopathogenicity.

ECHO 9 virus was identified in cultures of monkey kidney cells by the recommended technique of the committee on ECHO viruses.[1] In each culture 75 to 250 tissue culture dose—50 (50 per cent infectious for tissue culture) of virus and 20 units of ECHO-9 neutralizing antibody, as monkey antiserum, were used. Cultures were incubated at 37° C. and observed for five days.

Neutralizing antibodies were quantitated in monkey kidney cell cultures. Antibody end points were taken as the highest dilution of human test sera that completely neutralized virus and prevented cell destruction.

Leukocyte counts were determined on as many subjects as possible.

The majority of clinical observations and procurement of laboratory specimens were performed by one of us (J. W. S.).

CASE SUMMARIES

CASE 1.—T. Z., a 3-year-old white boy, developed a sparse red facial rash on July 20. On July 22 his temperature was 102.4° F., and examination revealed a diffuse, fine, erythematous eruption on his head, torso, and arms. Additional physical findings included minimal conjunctivitis, pharyngitis, and anterior and posterior cervical lymphadenopathy. By July 23 the exanthem was fading, the temperature was normal, and he was feeling well. On July 22, the leukocyte count was 6,000 per cubic millimeter, with 66 per cent neutrophils and 28 per cent lymphocytes. ECHO 9 virus was isolated from a throat swab obtained on July 22 (d.o.i.-3).* Serologic study revealed an 8-fold rise in titer of neutralizing antibody against ECHO 9 virus during a 28-day interval. There was no known prior exposure to a similar illness.

CASE 2.—B. Z., a 6-year-old white boy, became febrile on July 20. On July 22 examination revealed a temperature of 102° F. and a blotchy erythematous eruption most marked on the cheeks but scattered diffusely over the rest of the face; this was the day of onset of the exanthem. Additional findings were minimal conjunctivitis and anterior and posterior cervical lymphadenopathy. By July 23, the exanthem was fading, the temperature was normal, and he was feeling well. The leukocyte count was 8,500 per cubic millimeter, with 55 per cent neutrophils and 40 per cent lymphocytes. ECHO 9 virus was isolated from both a throat swab obtained on July 22 (d.o.i.-3) and a stool specimen obtained on July 31 (d.o.i.-12). Serologic study revealed an 8-fold rise in titer of neutralizing antibody against ECHO 9 virus during a 28-day interval. There was no known prior exposure to a similar illness.

CASE 3.—D. Z., a 5-year-old white girl, became febrile and had a temperature of from 100° to 101° F. on July 21. On July 22 examination revealed normothermia and a blotchy erythematous eruption most marked on the cheeks plus a fine, pink, papular eruption near the hairline and scattered over the torso and extremities. Additional findings included minimal conjunctivitis and anterior and posterior cervical lymphadenopathy. By the next day, July 23, the exanthem was already fading. On July 22 the leukocyte count was 11,150 per cubic millimeter, with 41 per cent neutrophils and 51 per cent lymphocytes. ECHO 9 virus was isolated from a throat swab obtained on July 22 (d.o.i.-2). Unfortunately, it was realized too late that the convalescent-phase serum sample

*(d.o.i.-3) represents the third day of illness.

had been misplaced so that confirmatory serologic studies could not be performed. There was no known prior exposure to a similar illness.

Comment.—It is interesting to note that CASE 1 (T. Z.) experienced 48 hours of rash before fever ensued.

To illustrate the familial epidemiology of this infectious exanthem (T. Z., B. Z., and D. Z. being siblings), we might add the case of M. Z. The latter, an infant, coincident with the illness of his siblings, developed an 101° to 102° F. fever for two days, followed by a fine, erythematous, papular eruption on his head, torso, and extremities which lasted three days. Viral investigation was not undertaken in this child. Three days after the onset of the rash in her children Mrs. Z. was afflicted with fever, headache, meningismus, and malaise requiring hospitalization. Mrs. Z. had a 64-fold rise in titer of neutralizing antibody against ECHO 9 virus during a 22-day interval. Mrs. Z. had no rash.

With so consistent a family sequence of ECHO 9 virus infection, we felt little compunction about including CASE 3 (D. Z.) in our exanthem study despite lack of serologic confirmation.

CASE 4.—R. K., a 4½-year-old white boy, developed a fever of 101° to 102° F. on July 31 which remitted on August 1 only to be followed on the same day by a mild, erythematous, maculopapular facial rash. Two days later the eruption was gone. ECHO 9 virus was isolated from both a throat swab obtained on August 3 (d.o.i.-4) and a stool specimen obtained on August 5 (d.o.i.-6). This child had a 32-fold rise in titer of neutralizing antibody against ECHO 9 virus after only 18 days. There was no known prior exposure to a similar illness.

CASE 5.—D. K., a 2½-year-old white boy, developed a fever of 100° F. on July 25 plus anorexia and malaise. On July 26 his temperature rose to 101° to 102° F., and the following day he had an erythematous maculopapular rash on the face and extremities, sparing the torso. The eruption lasted only 48 hours. It is not known whether the fever persisted after the onset of the rash. ECHO 9 virus was isolated from throat swabs obtained on July 28 (d.o.i.-4) and August 3 (d.o.i.-10). An 8-fold rise in titer of neutralizing antibody against ECHO 9 virus occurred after 24 days. There was no known prior exposure to a similar illness.

CASE 6.—M. K., a 1½-year-old white boy, developed a very mild fever on July 29 followed on July 30 by an erythematous maculopapular eruption on the face and arms, most markedly the former. The rash had disappeared by August 1, two days later. ECHO 9 virus was isolated from a fecal specimen obtained on August 3 (d.o.i.-6). No serologic studies were available. There was no known prior exposure to a similar illness.

Comment.—Again the pleotrophism and invasiveness of this virus are demonstrated by the appearance of fever, headache, and stiff neck in the mother of the three siblings cited above. She did not develop a rash. A 32-fold rise in titer of neutralizing antibody against ECHO 9 virus constituted proof of ECHO 9 virus infection. Mrs. K.'s symptoms followed those of CASE 5 (D. K.) by 12 days and CASE 4 (R. K.) by 5 days. Such a sequence suggests an incubation period of from 5 to 12 days. No infectious exposure other than to her children was known to this mother.

CASE 4 (R. K.) had an interesting "roseoloid" pattern of infection as fever and the lysis of same preceded his eruption.

CASE 7.—D. F., a 7-year-old white boy, became ill with fever, vomiting,

and diarrhea on July 21 and was admitted to the University of Minnesota Hospitals on July 23 as having a "fever of unknown origin." Abdominal pain, nausea, and dizziness continued until July 26, at which time a sparse, fine, erythematous rash appeared on his torso. The exanthem lasted 48 hours. Fever persisted until July 27, becoming as high as 103° F. Examination on the day of onset of the rash revealed an injected pharynx and anterior cervical lymphadenopathy. On the day of admission, July 23, three days prior to the eruption, the leukocyte count was 8,100 per cubic millimeter, with 90 per cent neutrophils and 10 per cent lymphocytes. ECHO 9 virus was isolated from a throat swab obtained on July 27 (d.o.i.-7) and a stool specimen obtained on July 31 (d.o.i.-11). A 4-fold rise in titer of neutralizing antibody against ECHO 9 virus was observed after a 32-day interval.

CASE 8.—E. G., a 3-year-old white girl, awakened the morning of August 18 with a discrete erythematous rash on her arms and a fever of 101° F. In 12 hours the eruption had spread gradually to her neck, chest, and legs, and her temperature had risen to 103° F. She also became anorexic and vomited several times. When seen the following day, August 19, a "rubelliform" eruption was noted over the chest, upper back, abdomen, and all extremities. A fine, pink rash appeared on the face, most marked over the malar eminences. Mild pharyngeal injection and posterior cervical lymphadenopathy were also observed. The entire illness lasted only 48 hours. ECHO 9 virus was isolated from a fecal specimen obtained on August 20 (d.o.i.-3). An 8-fold rise in titer of neutralizing antibody against ECHO 9 virus occurred after a 30-day interim.

CASE 9.—M. McH., a 9-year-old white girl, developed a fever of 100.3° F. on August 15. The following day her temperature was 101° F., and on August 17 a diffuse, fine, macular, red rash appeared on her cheeks, torso, and extremities. She also had slight pharyngeal injection and anterior and posterior cervical lymphadenopathy. The exanthem disappeared after only one day. Fever, however, persisted until August 20, two days after the rash had vanished. The temperature varied from 101° to 102° F. Anorexia, vomiting, and lethargy were prominent symptoms throughout the duration of the eruption. A leukocyte count taken at the time of the rash was 4,750 per cubic millimeter, with 60 per cent neutrophils and 35 per cent lymphocytes. ECHO 9 virus was isolated from both a throat swab obtained on August 19 (d.o.i.-5) and a stool specimen obtained on August 22 (d.o.i.-8). Serologic study revealed a 4-fold rise in titer of neutralizing antibody against ECHO 9 virus attained after a 28-day interval.

CASE 10.—R. K., a 10-month-old white boy, became febrile on July 20 and had a temperature recording of 101° F. Emesis occurred on the same and following day. On July 22 a diffuse, fine, red rash appeared, which spread over his entire body. Two days later the eruption was "heavier and thicker." By July 29 the exanthem was reported to be fading. Fever continued throughout the period of the eruption. Minimal conjunctivitis and pharyngitis were noted as well as posterior cervical lymphadenopathy. A leukocyte count on July 23 was 10,300 per cubic millimeter, with 45 per cent neutrophils and 55 per cent lymphocytes. ECHO 9 virus was isolated from a throat swab performed on July 24 (d.o.i.-7). Specimens for serologic proof of ECHO 9 virus infection were not obtainable.

Comment.—The preceding four cases all manifested gastrointestinal disturbance, primarily vomiting, as the symptom either prodromal to, or concomitant with, the exanthem. One might suggest that, akin to the respiratory tract involvement in rubeola and rubella, in the ECHO 9 exanthem the gastrointestinal tract is the site of the associated "catarrh."

Noteworthy was the prolonged prodrome prior to the appearance of the evanescent rash in CASE 7 (D. F.). By contrast, in CASE 8 (E. G.) the exanthem and associated clinical phenomena appeared simultaneously, similar to the pattern of rubella.

We feel that the inclusion of CASE 10 (R. K.) despite lack of serologic data is justifiable for two interesting reasons. First, during an epidemic of aseptic meningitis in New York due to ECHO 6 virus, a 58 per cent yield of virus was obtained from the throats of symptomatic subjects, while by contrast, not one virus was isolated from the pharynx of an asymptomatic, mere household contact.[19] Second, in a similar outbreak in Belgium due to ECHO 9 virus, a 50 per cent yield from the throats of patients was obtained only between the first and fourth day of the illness and nothing thereafter. However, there was a 16 per cent yield from stool specimens and a 20 per cent yield from spinal fluid after even the fifteenth day.[13] Albeit inferential, we feel a positive viral isolate from the pharynx is of etiologic significance, such was true in CASE 10 (R. K.).

CASE 11.—H. B., a 33-year-old white man, a pediatrician, developed a temperature of 103° F. on July 27, which lasted three days. Simultaneously he had a headache and malaise for three days. On July 28 a faint rubelliform rash appeared on his chest and then spread to the arms and thighs. The eruption abated after three days. ECHO 9 virus was isolated from a throat swab taken on July 31 (d.o.i.-4), and serologic investigation revealed a 4-fold rise in titer of neutralizing antibody against ECHO 9 virus after 14 days.

CASE 12.—M. B., a 35-year-old white woman, wife of H. B. and also a physician, developed a fever of 104° F. on July 27 (the same day as her husband). Her febrile response continued seven days thereafter as a low grade fever of 100° F. She also suffered from a headache and malaise for three days, these symptoms plus fever all began simultaneously. On July 28 a diffuse scarlatiniform rash occurred, but disappeared in 24 hours. Four days later, on August 1, the rash recurred as a faint maculopapular eruption on the face, torso, arms, and thighs, again lasting only 24 hours. ECHO 9 virus was isolated from a throat swab obtained on August 1 (d.o.i.-5). After a 20-day period, an 8-fold rise in titer of neutralizing antibody against ECHO 9 virus was observed.

CASE 13.—S. R., a 23-year-old white woman, a registered nurse, noted the onset of an undetermined degree of fever plus headache and malaise on July 21. Three days later, a petechial red rash was seen on the lower legs; soon afterward a rubelliform eruption appeared on the face and torso. On July 26 examination revealed a mild diffuse erythema over the left malar eminence plus 2 to 3 mm. pink "spots" scattered liberally over the torso and minimally on the legs. Slight pharyngeal redness was also recorded. By July 28 the exanthem and accompanying symptoms vanished. A leukocyte count performed at the height of the rash was 4,500 per cubic millimeter, with 50 per cent neutrophils and 39 per cent lymphocytes. Both a throat swab obtained on July 25 (d.o.i.-5) and a fecal specimen obtained on August 1 (d.o.i.-12) yielded ECHO 9 virus. An 8-fold rise in titer of neutralizing antibody against ECHO 9 virus occurred after 19 days.

Comment.—The biphasic eruption observed in CASE 12 (M.B.) is unique and similar to the sequence seen in erythema infectiosum.[20]

Four days before the onset of the ECHO 9 exanthem in CASES 11 and 12 (H. B. and M. B.), their 14-month-old son developed fever, malaise, anorexia, and rash.

TABLE I. CLINICAL STUDY OF ECHO 9 EXANTHEM

STUDY SUBJECT	AGE (YEARS)	SEX	EXANTHEM PRODROMATA	EXANTHEM DURATION (DAYS)	FEVER	CLINICAL AND LABORATORY OBSERVATIONS					WHITE BLOOD COUNT NEUTROPHILS/ LYMPHOCYTES
						PHARYNGITIS	CONJUNCTIVITIS	ADENOPATHY	EMESIS	DIARRHEA	
T. Z.	3	M	None	4	102° R.	Minimal	Minimal	Anterior and posterior cervical	None	None	6,000 66/28
B. Z.	6	M	Fever for two days	2	102° O.	None	Minimal	Anterior and posterior cervical	None	None	8,500 55/40
D. Z.	5	F	Fever for one day	2	101° R.	None	Minimal	Anterior and posterior cervical	None	None	11,150 41/55
R. K.	4½	M	Fever for one day	2	102° R.	None	None	None	None	None	—
D. K.	2½	M	Fever, anorexia, and malaise for 2 days	2	102° R.	None	None	None	None	None	—
M. K.	1½	M	Fever for one day	2	Present, but not recorded	None	None	None	None	None	—
D. F.	7	M	Fever, emesis, diarrhea and abdominal pain for 5 days	2	103° R.	Minimal	None	Anterior cervical	Present	Present	8,100 90/10
E. G.	3	F	None	2	103° R.	Minimal	None	Posterior cervical	Present	None	
M. McH.	9	F	Fever for two days	1	102° R.	Minimal	None	Anterior and posterior cervical	Present	None	4,750 60/35
R. K.	10 months	M	Fever and emesis for 2 days	7	101° R.	Moderate	Minimal	Posterior cervical	Present	None	10,300 45/55
H. B.	33	M	Fever, headache, and malaise for 1 day	3	103° O.	None	None	None	None	None	—
M. B.	35	F	Fever, headache, and malaise for 1 day	1	104° O.	None	None	None	None	None	—
S. R.	23	F	Fever, headache, and malaise for 3 days	3	Present, but not recorded	Minimal	None	None	None	None	4,500 50/39

Eight days after the onset of illness in CASE 13 (S. R.), her husband complained of malaise, and subsequently there appeared a faint morbiliform rash sparing only the face. Assuming a similar viral etiology in this instance, an 8-day incubation period was suggested.

Nonspecific malaise was the complaint of 4 out of 13 subjects, and headache was cited in only the 3 adults, CASES 11 to 13. Gastrointestinal symptoms were observed in 4 of the children, all 4 experienced emesis and 1 of the 4 also complained of abdominal pain and diarrhea. When these symptoms were

TABLE II. VIROLOGIC AND SEROLOGIC STUDIES OF ECHO 9 EXANTHEM

STUDY SUBJECTS	ECHO 9 VIRUS ISOLATIONS BY DAY OF ILLNESS (DOI)				SERUM NEUTRALIZING ANTIBODY RESPONSES TO ECHO 9 VIRUS			
	THROAT SWABS		STOOLS		ACUTE-PHASE SERA		CONVALESCENT-PHASE SERA	
	POSITIVE (D.O.I.)	NEGATIVE (D.O.I.)	POSITIVE (D.O.I.)	NEGATIVE (D.O.I.)	(D.O.I.)	TITER	(D.O.I.)	TITER
T. Z.	3	--	*	*	3	10	31	80
B. Z.	3	--	12	--	3	10	31	80
D. Z.	2	--	*	*	†	--	†	--
R. K.	4	23	6	--	4	4	22	128
D. K.	4, 10	29	*	*	4	10	28	80
M. K.	-	25	6	--	†	--	†	--
D. F.	7	--	11	9	7	10	39	40
E. G.	-	2	3	--	2	10	32	80
M. McH.	5	6	8	13	5	10	33	40
R. K.	4	--	*	*	†	--	†	--
H. B.	4	--	*	*	4	10	18	40
M. B.	5	--	*	*	4	10	24	80
S. R.	5	--	12	10	5	10	24	80

Specimens were tested in monkey kidney cells, HeLa cells, human amnion cells, foreskin fibroblast explant cultures, and litters of 1- to 2-day-old mice.

Neutralizing antibody titers are given at the highest dilution of serum that completely neutralized 75 to 250 TCD—50 (tissue culture dose) of ECHO 9 virus from subject H. B. when tested in cultures of monkey kidney cells. These results were confirmed by repeated tests.

*Stool specimens were not obtained.

†Sera were either lost or unable to be obtained.

DISCUSSION OF THE CLINICAL AND LABORATORY OBSERVATIONS

The data mentioned in the preceding clinical summaries are tabulated in Tables I and II.

Eight males and 5 females comprised our series of patients. The group consisted of 1 infant, 6 children 1 to 5 years old, 3 youngsters 6 to 10 years of age, and 3 adults.

Fever was present in all the subjects as a symptom either prodromal or concurrent with the rash. At its height, the fever ranged from 101° to 104° F., the usual temperature elevation being 102° F. The fever persisted from 1 to 8 days, the average being 3½ days. actually prodromal to the rash, they occurred from 0 to 5 days before the exanthem appeared. The average duration of this phase was about 1½ days.

The exanthem lasted from 1 to 7 days, with the usual duration being 2½ days.

The distribution of the eruption was rather interesting as the face and occasionally the cheeks alone seemed to be the most common site. Eleven of the 13 subjects had a facial rash, 5 of these 11 exhibited the eruption only on the cheeks. Two youngsters, CASES 2 (B. Z.) and 4 (R. K.), had just a facial rash. The torso and arms were involved in 9 out of the 13 patients

The legs were the least commonly involved, only 7 of the 13 individuals demonstrated an eruption in this region. CASE 7 (D. F.) was unique in that only the torso was covered.

Summarizing the clinical descriptions of this exanthem, one could morphologically characterize it as rubelliform in appearance, an impression also forwarded by others.[8, 17]

Additional physical findings included pharyngitis in 6, conjunctivitis in 4, and cervical adenopathy in 7 subjects.

As might be inferred from the clinical summaries, this illness was for the most part very mild.

Leukocyte counts varied from 4,500 to 11,000 per cubic millimeter, with from 41 to 90 per cent neutrophils and from 6 to 55 per cent lymphocytes.

Eleven of the 13 (85 per cent) cases studied yielded a throat swab positive for ECHO 9 virus (see Table II). One-hundred per cent of the subjects from whom a stool specimen was procured carried ECHO 9 virus in their gastrointestinal tract. Positive throat cultures were obtained as late as the tenth day of illness. CASES 8 (E. G.) and 9 (M. McH.) had negative throat swabs on the second and sixth day of illness, respectively. Three other negative throat swabs occurred after the twenty-second day of illness. Positive stool cultures were obtained as late as the twelfth day of illness. Three negative cultures occurred on the ninth, tenth, and thirteenth days of illness, and in two of these instances a positive stool culture was obtained two days later. A significant rise in titer of neutralizing antibody versus ECHO 9 virus took place in all of the ten subjects so studied.

As mentioned above, from study subject and family member temporal relationships, the incubation period of this infectious exanthem seems to be approximately one week.

DIFFERENTIAL DIAGNOSIS

When the early cases were seen they were thought to be the Boston Exanthem. This is a summer rash, rubelliform in appearance, noted predominantly on the face and torso, and lasts from 2 to 4 days. After an incubation period of about one week, either the exanthem itself or a short prodrome of fever ensues.[2-4] Sore throat, headache, abdominal pain, anorexia, conjunctivitis, and cervical adenopathy are occasionally observed. The marked similarity between the Boston Exanthem and our cases is quite obvious.

Severe miliaria rubra was an initial consideration in a few cases, but fever, pharyngoconjunctivitis, and cervical adenopathy served to clarify the clinical impression.

Morbilliform drug eruptions should always be eliminated. A history of drug administration, the descending pattern of the eruption with eventual involvement of palmar and plantar surfaces, and eosinophilia usually aid in establishing a correct diagnosis.

It was our impression that this exanthem was often called atypical rubella. The usual paucity of prodromal symptoms, the presence of postauricular and suboccipital lymphadenopathy, and the concentration of rash on the torso should differentiate rubella from ECHO 9 virus exanthem.[21]

As mentioned above, one of our cases manifested a sequence of fever and rash which resembled roseola.

However, one should not anticipate that "a clinical syndrome so clear and distinct"[22] will often be confused with the cases described in this paper.

As virologic techniques improve and the search for viral-caused diseases continue, many other ill-defined eruptions will also be unraveled. The curious clinician has a unique opportunity to implement the solution of many such puzzles.

SUMMARY

Thirteen cases of a summer rubelliform exanthem are presented in considerable detail plus virologic evidence of causation by ECHO virus type 9. Fever, malaise, and gastrointestinal symptoms antedated or coincided with the onset of a rash which lasted from 2 to 3 days and involved, primarily, the face, arms, and torso. Pharyngitis, conjunctivitis, and cervical lymphadenopathy were occasional accompanying physical findings. The total leukocyte count and differential were usually within normal limits. An incubation period of approximately one week was apparent from case observations within several families.

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THE USE OF WEEKLY ORAL DOSES OF SULFAMETHOXYPYRIDAZINE FOR RHEUMATIC FEVER PREVENTION

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PREVENTION of recurrent attacks of rheumatic fever by continuous chemoprophylaxis against streptococcal infections is now a generally accepted procedure.[1] The choice of an antibiotic and its mode of administration requires further exploration, however, inasmuch as certain disadvantages continue to limit the efficacy of commonly accepted regimens.[2, 3] Although monthly injections of benzathine penicillin have been shown, in carefully controlled studies, to be superior to certain oral regimens of penicillin and sulfonamides,[3, 4] the quest for a more efficient oral regimen continues because of the limited acceptability of prolonged parenteral medication. There is general agreement that many of the failures of oral prophylaxis are due to forgetfulness on the patient's part to take medication daily.

Recently, a new sulfonamide compound, sulfamethoxypyridazine (Kynex*), was discovered to produce measurable blood levels as long as seven days after the administration of a single oral dose.[5, 6] It was considered of interest to explore the suitability of using this drug in single weekly oral doses as secondary prophylaxis of rheumatic fever. Preliminary observations by Lepper, Simon, and Marienfeld[6] indicated a good tolerance of such a regimen in a small closed population. In addition favorable results have been achieved with the use of this compound in mass prophylaxis of epidemic streptococcal infection in a military population.[7]

The present study was designed to confirm the tolerance of such a regimen, to determine the blood levels achieved at varying intervals following each dose, and to make detailed observations on a limited number of rheumatic fever outpatients receiving this regimen with regard to the incidence of clinical and subclinical streptococcal disease.

METHODS AND MATERIALS

The prophylactic regimen was initiated in 30 patients who had had a proved attack of rheumatic fever by Jones criteria[8] within a period of 5 years. There was no previous history of sulfonamide sensitivity in any of the patients. The distribution of age was 8 to 39 years; 5 patients were under 10 years of age, 19 were 10 to 20 years old, and 6 were over 20 years of age.

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*Kynex was supplied through the courtesy of Dr. Eugene Swanzey, Lederle Laboratories Division, American Cyanimid Company, Pearl River, N. Y.

Eight of the 30 patients in whom prophylaxis was initiated were being hospitalized during the acute stage of rheumatic fever*; the remaining 22 patients attended the outpatient clinic.† Baseline studies included complete blood count, urinalysis, erythrocyte sedimentation rate, test for C-reactive protein, and antistreptolysin O titer. Patients who weighed more than 100 pounds received 3 Gm. of sulfamethoxypyridazine as a single weekly oral dose, and patients less than 100 pounds in weight received 2 Gm.

All patients were examined weekly for the first 8 weeks, biweekly for the next 2 months, and monthly thereafter. The average period of follow-up was 11 months. Each patient was carefully questioned and observed regarding any symptoms or signs of toxicity, such as headache, rash, nausea, drowsiness, hematuria, etc.

Sulfonamide blood levels were determined in whole blood twice weekly for 5 to 13 weeks after each oral dose. In one group this was done at 1 and 5 days, and in the other group at 1 and 7 days. Mean blood levels and their range were sampled therefore at 1, 5, and 7 days after each weekly dose for a period of from 5 to 13 weeks (Table I). The blood concentration of free sulfonamide, calculated as sulfamethoxypyridazine, was determined by the method of Bratton and Marshall.[9]

The following laboratory tests were performed at each visit during the first two months of the study: urinalysis, complete blood count, throat cultures, antistreptolysin O titers, and blood sulfonamide level. Swabs of the throat were inoculated directly onto 5 per cent sheep's blood agar and were incubated overnight at 37° C. for isolation of beta hemolytic streptococci. Hemolytic streptococci were classified as to serologic group and type by standard methods.[10] Erythrocyte sedimentation rates (ESR) were measured by the method of Wintrobe. Tests for the presence of C-reactive protein (CRP) were carried out by the method of Anderson and McCarty.[11] Determinations of the serum titer of antistreptolysin O were made by the method of Rantz and Randall,[12] with minor modifications. Changes in the level of a specific antibody were confirmed by testing stored serum samples which were obtained serially from the same patient and simultaneously on the same day. A rise in titer of two dilution increments in the antistreptolysin O tests was considered significant.

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RESULTS

Observations were completed on 30 patients for a total of 247-patient months. The mean follow-up period was 11 months. Fourteen patients were followed on this regimen for more than 1 year and 12 for less than 6 months. Nine patients received 2 Gm. of sulfamethoxypyridazine once weekly and 21 received 3 Gm.

Blood Levels.—Sulfonamide blood levels determined at 1, 5, and 7 days after each weekly dose in the same group of 21 patients are illustrated in Table I. Of 24 patients studied at 24 hours after drug administration, all had measurable blood levels each week they were studied. These levels ranged from 7 to 24 mg. per cent with a mean 24-hour level of 14.2 mg. per cent. Of 12 patients studied at 5 days after each weekly dose, all but 1 patient had measurable sulfonamide levels. The mean sulfonamide level at 5 days was

TABLE I. KYNEX BLOOD LEVELS* AT DAYS INDICATED FOLLOWING A SINGLE ORAL DOSE ADMINISTERED WEEKLY TO A GROUP OF RHEUMATIC FEVER PATIENTS FOR PERIODS OF 5 TO 13 WEEKS

WEEK AFTER FIRST DOSE	DAY 1 (24 HOUR BLOOD LEVEL)				DAY 5				DAY 7					
	NUMBER OF PATIENTS TESTED	NUMBER OF PATIENTS WITH BLOOD LEVELS	BLOOD LEVELS (MG. PER CENT)		NUMBER OF PATIENTS TESTED	NUMBER OF PATIENTS WITH BLOOD LEVELS	BLOOD LEVELS (MG. PER CENT)		NUMBER OF PATIENTS TESTED	NUMBER WITH <0.5 MG. PER CENT	NUMBER WITH >0.5 MG. PER CENT	NUMBER WITH LEVEL	BLOOD LEVELS	
			RANGE	AVERAGE			RANGE	AVERAGE					RANGE	AVERAGE
1	15	15	6.5-19.6	12.9	9	8	0-5.3	2.0	8	1	2	3	0-1.9	1.3
2	11	11	11.4-22.4	15.1	9	9	1.3-5.9	3.1	9	3	6	9	0-0.8	0.6
3	10	10	11.4-24.6	15.5	8	8	<0.5-5.0	2.8	10	4	4	8	0-0.7	0.6
4	8	8	9.7-22.3	14.6	9	9	1.0-5.5	3.0	10	3	7	10	0-2.0	0.8
5	8	8	11.5-22.1	14.6	6	6	0.7-5.6	2.7	9	5	4	9	0-0.9	0.7
6	6	6	7.8-21.1	14.3					3	2	1	3	0-0.6	0.6
7	2	2	12.4-13.2	12.8					2	2	0	2	----	--
8	2	2	12.0-12.5	12.2					2	0	2	2	0-0.9	0.7
9	1	1	11.2	11.2					0	0	0	0	----	--
10					1	1	4.3	4.3	1	0	1	1	0-0.9	0.9
11									1	0	1	1	0-0.9	0.9
12									0	0	0	0	----	--
13					1	1	2.1	2.1	2	1	1	2	0-0.5	0.5
Total	63	63	6.5-24.6	14.2	43	42	0-5.9	2.8	57	21	29	50	0-2.0	0.7

The total number of patients was 30.
Dosage: over 100 pounds, 3 Gm., under 100 pounds, 2 Gm.
*Levels were determined on oxylated blood.

2.8 mg. per cent, with a range of from 0 to 5.9 per cent. Of twelve studied at 7 days, observations were made on 57 blood samples. Twenty-one of the 57 determinations showed measurable levels (greater than 0.5 mg. per cent). The mean was 0.7 mg. per cent. An additional 21 determinations showed traces of sulfonamides which could not be measured accurately. Seven determinations showed no detectable sulfonamide.

There were no indications that the levels were cumulative in any patient during the period they were given. By the twelfth week of the study, the levels determined at 1, 5, and 7 days were no greater than those measured during the first week of the study.

Toxicity.—No side effects were observed in the 9 patients receiving 2 Gm. daily. In the group receiving 3 Gm. of Kynex weekly, drowsiness and headache were the only significant side reactions. Eight of the patients reported drowsiness and 3 complained of a headache which began a few hours after their dose. One adult patient complained of headache and drowsiness on two consecutive visits, and the drug was discontinued at the patient's request. In the other 7 patients the time of administration of the drug was changed from morning to bedtime. Subsequently, no drowsiness was noted by any patient the following morning. One patient developed a faint macular rash which appeared on the extremities

TABLE II. SUMMARY OF KYNEX STUDY

I. *Patient Statistics:*	
Total number of patients followed	30
Total number of patient months observations were made	247
Average patient years	20
II. *Age:*	
6-10 years	5
10-15 years	8
16-20 years	11
20 years	6
III. *Kynex dosage:*	
2 Gm. once weekly (under 100 pounds)	9 (patients)
3 Gm. once weekly (over 100 pounds)	21 (patients)
IV. *Kynex Blood Levels During First 5 to 13 Weeks:*	
A. Total number of patients tested	25
B. Number of patients with blood levels tested at:	
3-4 hours	2/2*
24 hours	15/15
5 days	11/11
7 days	16/16
V. *Toxicity to Kynex:*	
Number of patients with clinical symptoms	10
Drowsiness	8
Headache	3
Abnormal CBC and urinalysis	0
Transient rash	1
VI. *Streptococcal Infections Acquired During Kynex Study:*	
Positive group A throat culture	0
ASO rise (significant)	3
ASO rise (questionable)	3
Clinical symptoms of sore throat	0

*Numerator equals the number of patients with detectable sulfonamide levels. Denominator equals number listed.

approximately 8 hours after ingestion of the drug and disappeared in 24 hours. Kynex was discontinued for one week. Readministration of sulfamethoxypyridazine produced no further rash or other side effects for the subsequent 9-month period.

There were no significant variations in the hemoglobin and white blood counts made routinely during the first 15 weeks, and there were no hemorrhagic manifestations. Urinalyses were unremarkable throughout the study.

Incidence of Streptococcal Infection.—During the 247-patient months of this study, no patient was found to have acquired group A streptococcus organisms in their throat. Two patients were found to be carrying group A streptococci on admission to the study. Following eradication of the organisms with a single injection of 1.2 million units of benzathine penicillin intramuscularly, the weekly regimen of oral Kynex was initiated, and no subsequent positive throat cultures were encountered. Six patients manifested a rise greater than 0.2 in the logarithm of the titer of antistreptolysin O during the course of the study; of these, 3 had a rise which did not exceed a titer of 125 units per milliliter. The fourth patient had an antistreptolysin O rise from less than 50 up to 200 units; the fifth patient had a rise of from 125 to 625 units; the sixth patient had a rise from less than 50 units up to 250 units. There were no recurrences of rheumatic fever.

DISCUSSION

The preliminary observations reported here encourage more extensive exploration of the use of weekly doses of Kynex as a prophylactic regimen in rheumatic fever patients. The lack of significant toxicity or of drug accumulation over these prolonged periods of administration suggest that the regimen may be sufficiently safe for more extensive trial, and this view is supported by the low toxicity reported by others.[5, 6, 13, 14] Lepper, Simon, and Marienfeld[6] studied a group of 38 children convalescing from rheumatic fever who received Kynex once weekly in a dose of 30 mg. per kilogram. Twenty-eight of the patients lived in the protected environment of a convalescent home. Measurable sulfonamide blood levels of 1.8 mg. per cent were obtained 7 days after a weekly dose. The drug was well tolerated. Several patients had transitory headaches, but this effect disappeared with later doses. It was not necessary to discontinue the drug in any patient because of toxicity. In this group of patients the low risk of contact with streptococcal disease made the evaluation of protection against streptococcal infection difficult.

In a well-controlled study Schultz and Frank[7] reported significant protection against streptococcal infections following the administration of a single weekly dose of sulfamethoxypyridazine for mass prophylaxis during a streptococcal epidemic.

The observations made on the incidence of streptococcal infection in the present study were only incidental to the main purposes, namely, determination of tolerance and of blood levels. The relative effectiveness of this regimen in preventing streptococcal disease cannot be appraised without an extensive comparison with matched groups of patients who received one of the conventional daily oral sulfonamide regimens.

Finally, the extensive use of other sulfonamides has been attended by occasional serious reactions, and Kynex appears to be no exception. Thus, focal hepatitis,[15] leukopenia, and thrombocytopenia[16] have been observed. Usually, however, these have occurred with much larger doses than those employed in this study. Extensive prophylactic use of this compound should not yet be undertaken, in our opinion, without adequate facilities for careful follow-up observations and appropriate laboratory studies.

SUMMARY

Sulfamethoxypyridazine (Kynex) was given once weekly in a single large oral dose to 30 patients for 247-patient months. The drug was well tolerated by all patients with the exception of occasional mild and transient side reactions of drowsiness and headaches. These observations warrant extension of the use of single oral weekly doses of sulfamethoxypyridazine to a larger number of rheumatic fever patients and comparison with similar patients receiving conventional daily oral prophylactic regimens.

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INTRAVENOUS CHLORAMPHENICOL IN SERIOUSLY ILL INFANTS AND CHILDREN

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THE purpose of this study was to evaluate intravenous chloramphenicol in pediatric practice with particular reference to clinical effectiveness, patient's tolerance, side effects, and toxicity.

In treatment of severe infections it is desirable to obtain effective blood and tissue levels as rapidly as practicable. High chloramphenicol blood levels are obtained within 5 minutes[1] after intravenous injection. Peak levels after oral or intramuscular administration of comparable doses are obtained only after 1½ to 2 hours.[1-4] Serum levels 3 hours after intravenous injection are slightly higher than after the same oral doses. At 12 and 24 hours they are about twice as high as those after the same single oral dose. After comparable doses of intramuscular chloramphenicol, serum levels do not appear to be adequate for therapy of some infections in older children and adults.[3] Within the near future, it is expected that a new form, chloramphenicol acid succinate, will be available. Experience thus far indicates that intramuscular administration of this form provides considerably higher serum concentration than does the crystalline form generally available at present.

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The principal objection to intravenous injection has been crystallization of the drug upon its preparation. Careful attention to details will regularly avoid this. It is not difficult, but it was found to be essential to adhere strictly to the following procedure. The intravenous preparation called Chloromycetin Solution is supplied in 2 c.c. ampules each containing 500 mg. of chloramphenicol in 50 per cent aqueous solution of N, N-dimethylacetamide. The *ampule should be warmed to body temperature.* We have done this by holding the ampule in the closed palm of the hand for 3 or 4 minutes. The contents should be withdrawn with a *dry* syringe and needle. Using *another dry needle*, it should be added rapidly to the diluent with the *tip of the needle under the surface of the diluent.* Sterile aqueous diluent such as physiologic salt solution or 5 per cent dextrose solution may be used. The *diluent should be at room temperature.* The *volume of the diluent should be at least 100 c.c. but no more than 250 c.c.* In order to inject beneath the surface of the diluent, it is best to insert the needle through the diaphragm of the upturned bottle containing the diluent. The addition should be done as *rapidly as the plunger of the syringe can be pushed by hand.* This dilute solution must be used immediately after preparation.

The usual rate of intravenous injection is 2 to 5 c.c. per minute and should not exceed 20 c.c. per minute.

MATERIALS AND METHODS

One hundred and seven pediatric patients were given intravenous chloramphenicol. Their ages ranged from 3 days to 13 years. The diseases exhibited in this group were: meningitis (67 cases), infectious diarrhea (13), respiratory tract infection (10), poliomyelitis (6), encephalitis (2), miscellaneous infection (5), and noninfectious diseases (4).

All patients in this study were so ill that they could not take oral medication.

Twenty patients received chloramphenicol by intravenous route only. The majority (80 patients) received the drug by intravenous route first and later orally. Four received it intravenously and later intramuscularly only and 3 by intravenous and later by intramuscular and oral routes.

The intravenous dosage varied from 16.5 to 175 mg. (average 69 mg.) per kilogram of body weight per day and was given in divided doses. It was given every 6 hours in 77 patients, every 8 hours in 13, and every 12 hours in 9 patients. In 2 patients it was given every 8 hours and then changed to every 6 hours. In one patient it was given every 12 hours and then changed to every eight hours. Five patients received only one dose by the intravenous route.

The number of intravenous injections per patient varied from 1 to 38 (average 10.5 injections) during a 6-hour to 10-day period (average 3 days). The duration of chloramphenicol therapy including all routes ranged from 6 hours to 24 days (average 9.5 days).

Cultures were taken routinely before the start of the therapy, and in the majority follow-up cultures were obtained.

Clinical evaluation was based on 91 patients, the following were excluded 4 whose meningitis was later determined to be tuberculous; 4 patients who were later determined to have noninfectious diseases; 6 with poliomyelitis; 2 with encephalitis. These 16 patients were included only in the study of tolerance, side effects, and toxicity.

In evaluation of clinical responses the cases were divided into two groups: one given chloramphenicol alone and the other given chloramphenicol plus one or more other antibacterial agents at the same time. Of the 91 patients, 48 received chloramphenicol alone and 43 chloramphenicol plus other antibacterial agents.

The following arbitrary classification of response was considered only as a means of describing the response and not as having statistical significance. A patient was considered unimproved if fever persisted or cultures remained positive or if he remained clinically ill or died during chloramphenicol therapy. The patient was classed as unimproved if favorable clinical response occurred only after chloramphenicol was discontinued and another drug started. The responses in improved cases were graded excellent, good, or fair; excellent when the patient became afebrile within 3 days of therapy, good when the patient became afebrile after 3 days but within 5 days, and fair when the patient became afebrile only after 5 days of chloramphenicol therapy.

RESULTS

Of the 91 patients evaluated for clinical response (Table I), 76 improved and 15 were unimproved as defined above. Of the latter 15, 7 died. Of the improved patients, 46 had excellent responses, 22 good, and 8 fair. Of the 76 improved patients, 43 received chloramphenicol alone and 33 received chloramphenicol plus other drugs simultaneously (Table I). Of the unimproved patients, 5 received chloramphenicol alone and 10 received chloramphenicol plus other antibacterial drugs simultaneously. The number of days for the improved patients to become afebrile after the start of intravenous chloramphenicol ranged from 4 hours to 12 days (average 3 days).

TABLE I. CLINICAL RESPONSE TO CHLORAMPHENICOL

DISEASES	TOTAL NUMBER OF CASES	IMPROVED PATIENTS — CHLORAMPHENICOL			UNIMPROVED PATIENTS — CHLORAMPHENICOL		
		ALONE	WITH OTHER DRUGS	TOTAL	ALONE	WITH OTHER DRUGS	TOTAL
Meningitis influenzal	43	27	13	40	1 (1)	2 (2)	3 (3)
Meningococcal	4	—	3	3	—	1	1
Penumococcal	2	—	—	—	—	2 (1)	2 (1)
Other types	14	5	8	13	—	1	1
Infectious diarrhea	13	5	4	9	2	2	4
Respiratory disease	10	5	1	6	2 (1)	2 (2)	4 (3)
Miscellaneous infection	5	1	4	5	—	—	—
Total	91	43	33	76	5 (2)	10 (5)	15 (7)

Figures in parentheses refer to deaths.

Hemophilus influenzae type b were isolated from the spinal fluid cultures of 43 patients. Twenty-four had positive blood cultures and one had a positive nasopharyngeal culture for this organism. The follow-up cultures were collected from 14 hours to 21 days after onset of therapy. Of these, there were 29 spinal fluid, 4 blood, and 8 nasopharyngeal cultures. All of the first two were sterile and all of the last were negative for this organism.

Forty of these patients improved (93 per cent) and 3 died. Of the 40 improved patients, 23 had an excellent response, 12 good, and 5 fair. Thirteen of the improved patients received chloramphenicol plus other antibacterial drugs simultaneously. Of the 27 improved patients who received chloramphenicol alone, 17 had an excellent response, 8 good, and 2 fair. Of those who received chloramphenicol plus other antibacterial drugs, 6 had an excellent response, 4 good, and 3 fair. One of these developed a subdural effusion. She had received sulfisoxazole and streptomycin together with chloramphenicol. She improved with repeated subdural taps. Two of the 3 who died had had their illnesses for 3 weeks before chloramphenicol was started, during which time they received other antibiotics (penicillin and oleandomycin in one and penicillin and oxytetracycline in the other). One received intravenous chloramphenicol for 36 hours before death, and the other received it for only 12 hours before death together with sulfadiazine and penicillin. The third patient who died was in moribund condition on admission to the hospital. He was sick for only 7 hours prior to admission and died after only 5 hours' stay in the hospital. During this 5-hour period, he received 1 dose of intravenous chloramphenicol and 1 dose of streptomycin and 2 of penicillin intramuscularly.

Neisseria intracellularis were isolated from the spinal fluid of 3 patients and were identified only by direct smear of the spinal fluid in 1

patient. The latter had received 2 doses of penicillin prior to examination. All of these patients were treated with chloramphenicol in combination with other antibacterial agents. Three responded excellently. A 3-month-old boy with this disease was classified as unimproved, having become afebrile only after another antibacterial agent was used. He was simultaneously given a combination of streptomycin, chloramphenicol, and sulfadiazine. The organism was sensitive in vitro to both chloramphenicol and penicillin. He was given 62 mg. per kilogram of body weight per day of intravenous chloramphenicol in 4 equally divided daily doses every 6 hours for 3 days, and then a small oral dose of 82 mg. per kilogram of body weight per day for 2 days. Fever and bulging fontanel persisted although the spinal fluid culture obtained on the fourth day of therapy was sterile. Subdural taps done on the fifth day of therapy were negative. Streptomycin was given for only one day. Chloramphenicol was discontinued on the fifth day, and sulfadiazine continued for a total of twelve days. Two days after discontinuance of chloramphenicol, penicillin was given. He became afebrile 9 days later and appears to have recovered completely. The reason for persistence of fever was not determined.

Pneumococcus group E, type 19 were isolated from the spinal fluid of two patients. Neither responded to chloramphenicol. One, a 10½-year-old boy, was treated with chloramphenicol and penicillin for 5 and 15 days, respectively. The organism was sensitive in vitro to penicillin and moderately sensitive to chloramphenicol. Chloramphenicol was given intravenously in a dosage of 63 mg. per kilogram of body weight per day in 4 equally divided doses every 6 hours. This treatment was continued intramuscularly for 4 days and by mouth for 1 day. Temperature became normal within 2 days and remained normal for 3 days. However, while still receiving this combination of chloramphenicol and penicillin, the patient developed a fever. On the sixth day after the start of therapy, the spinal fluid revealed gram-variable cocci which did not grow in culture. Chloramphenicol was discontinued and sulfadiazine started. The patient responded excellently and his temperature became normal 1 day later. The other patient had been ill for one week and died after only 12 hours in the hospital. During these 12 hours, she was given intravenous chloramphenicol and also penicillin and streptomycin.

Fourteen patients had other types of meningitis. *Salmonella typhimurium* were isolated from the spinal fluid, blood, and stool of 1 patient. Nonhemolytic streptococci were isolated from the spinal fluid of another. Eleven patients had purulent spinal fluid but sterile cultures. Of the latter 11, gram-negative rods (2 cases) and gram-positive bacilli (1 case) were found on direct smear of the spinal fluid. Seven of these 11 patients (including 1 with a positive smear for gram-negative rods) received other antibacterial drugs before examination. These drugs were sulfisoxazole, streptomycin, oxytetracycline, or sulfadiazine. Four of these 11 patients had received no other antibacterial agents before examination. One patient had mumps meningoencephalitis.[5] Thirteen of the 14 patients improved (Table 1). Seven had an excellent response and 6 good. Five of the improved patients received chloramphenicol alone and 8 received chloramphenicol plus other antibacterial drugs.

One of these patients did not respond. This 7-week-old boy had a severe nonhemolytic streptococcal meningitis. Symptoms began 12 hours before examination. The organism was sensitive in vitro to 0.15 μg per milliliter of chlortetracycline, 0.15 Oxford unit per milliliter of penicillin, and 2 μg per milliliter of chloramphenicol. He was given chloramphenicol intravenously for 3 days, sulfadiazine intravenously for 1 day,

subcutaneously for 5 days, and orally for 10 days, and procaine penicillin intramuscularly for 16 days. The intravenous dosage of chloramphenicol was 110 mg. per kilogram of body weight per day divided into 2 doses given at 12-hour intervals. A subdural effusion on the left side was found on the third day of therapy, at which time chloramphenicol was stopped. Subdural fluid was sterile. He gradually improved but strabismus persisted. During the next 6 months he developed convulsions, and he appeared to be retarded.

Stool cultures were obtained from each of the 13 patients with "clinically" infectious diarrhea before starting chloramphenicol therapy. One yielded *Salmonella typhimurium*, 2 Shigella flexneri IV boyd 103, 3 *Pseudomonas aeruginosa*, 2 *Proteus mirabilis*, 1 *Proteus morganii*, 1 paracolon, and 3 were not revealing. The blood culture of the patient with Salmonella was positive for the same organism. Of the 9 patients who improved, 6 had an excellent response, 2 good, and 1 fair (Table I). The organisms in the improved patients were Shigella (2 cases) and Salmonella, *Proteus morganii*, *Proteus mirabilis*, and paracolon, one each. The patients with Shigella and Salmonella infection improved rapidly with chloramphenicol alone. Within 9 days of therapy, the stool culture of one of the patients with *Proteus mirabilis* dropped from 80 to 10 per cent concentration of the fecal flora. The infant also improved rapidly clinically. The stool culture of the 4 patients who did not improve showed *Pseudomonas aeruginosa* in 3 and *Proteus mirabilis* in 1.

The 10 respiratory tract infections were in the form of pneumonia (9 cases) and laryngotracheobronchitis (1 case). The initial nasopharyngeal cultures showed as predominant organisms: *Micrococcus pyogenes* var. *aureus* in 6 patients, including the laryngotracheobronchitis, a mixture of *Micrococcus pyogenes* var. *aureus* and pneumococci in 1, a mixture of *Pseudomonas aeruginosa* and *Proteus mirabilis* in 1, coli aerogenes in 1 patient, and common nonspecific organisms in 1. Blood cultures in all were sterile. Five of the 6 improved patients were treated with chloramphenicol alone (Table I).

Of the 4 unimproved patients, 3 died (Table II). One 21-month-old girl had lobar pneumonia for 6 days and had not responded to penicillin. *Micrococcus pyogenes* var. *aureus* was isolated in pure culture from the nasopharynx. The organism was sensitive in vitro to chloramphenicol. Seventy milligrams of chloramphenicol per kilogram of body weight was given in 4 equally divided doses for 4 days. The child did not respond and the drug was discontinued. Chlortetracycline was then given with an excellent response.

All of the 5 patients with miscellaneous infections improved (Table I). They had: (1) orbital cellulitis secondary to sinusitis; (2) aphthous stomatitis with follicular tonsillitis, with an almost pure bacterial culture of *Micrococcus pyogenes* var. *aureus*; (3) superficial gangrene of cut-down site in a child with septicemia due to *Micrococcus pyogenes* var. *aureus*; (4) appendicial abscess; and (5) cellulitis with secondary ulceration of the chest wall. *Micrococcus pyogenes* var. *aureus* was obtained in pure culture from the drainage of the latter patient's wound. Four received other antibacterial drugs which may have contributed to the outcome.

DEATHS

Seven of the 91 patients who were subjected to clinical evaluation died. They had hemophilus influenzal meningitis (3 cases), pneumococcal meningitis (1 case), and bronchopneumonia (3 cases) (Table II). The first 5 cases received chloramphenicol for less than 36 hours before death. The sixth had severe cerebral palsy and bronchopneumonia and had been ill before admission for an undeterminable time.

TABLE II. DEATHS

AGE	SEX	DIAGNOSIS AND DURATION BEFORE CHLORAMPHENICOL	TREATMENT BEFORE CHLORAMPHENICOL	INTRAVENOUS CHLORAMPHENICOL		COMMENTS
				DOSAGE (MG./KG. BODY WEIGHT/DAY)	DURATION	
1 Year	F	Meningitis, *Hemophilus influenza* (3 weeks)	Penicillin and oxytetracycline (3 weeks)	92	36 hours	Chloramphenicol started too late
13 Months	F	Meningitis, *Hemophilus influenza* (3 weeks)	Penicillin (1 week), then oleandomycin (2 weeks)	67.5	6 hours	Chloramphenicol started too late. Patient already in moribund condition. Received sulfadiazine subcutaneously and penicillin at same time as chloramphenicol. Autopsy: meningitis and hydrocephalus.
2½ Years	M	Meningitis, *Hemophilus influenza* (7 hours)	None	80	5 hours	Moribund on admission. Died 5 hours later. Given streptomycin and crystalline penicillin at same time as chloramphenicol
5 Years	F	Meningitis, pneumococcal (3 weeks)	Chlortetracycline (1 week)	110	12 hours	Patient moribund when chloramphenicol started. Received penicillin and streptomycin at same time
3 Months	M	Bronchopneumonia (3 days). Blood, nasopharyngeal, and spinal fluid cultures were nonrevealing	Penicillin and streptomycin (2 days)	110	24 hours	Comatose when chloramphenicol was started. Penicillin and streptomycin also continued during chloramphenicol therapy. Autopsy: hemorrhagic bronchopneumonia, acute hepatitis, mesenteric lymphadenitis, and edema of brain
4 Years	M	Cerebral palsy and bronchopneumonia (4 days). Nasopharyngeal culture revealed only *Pseudomonas aeruginosa* and *Proteus mirabilis*	None	53	10 days	On tenth day of chloramphenicol therapy, the drug was stopped, and penicillin and streptomycin were given for 6 days, but to no avail
6 Years	F	Bronchopneumonia (9 days). Blood and nasopharyngeal cultures were noncontributory	Oxytetracycline (3 days), then erythromycin and streptomycin (3 days), then penicillin and streptomycin (1 day)	44 mg. at start, then reduced to 18 mg. on fifteenth day of illness	10 days	On ninth day of illness, myocarditis and heart failure; chloramphenicol given for 8 days with other drugs. Autopsy: bronchopneumonia with septicopyemic abscesses due to *Micrococcus Pyogenes* var. *aureus* in all internal organs (see text)

The seventh case was that of a 6-year-old girl who had had bronchopneumonia for 8 days. During this time, she did not respond to oxytetracycline, which was started on the second day of the illness and given for 3 days, followed by erythromycin and streptomycin given in combination for 3 days, and penicillin and streptomycin given in combination for 1 day. On the ninth day of illness, she developed myocarditis and heart failure. She was digitalized and given supportive treatment. A blood culture taken on the sixth day of illness was sterile, and only coli aerogenes were found in the nasopharyngeal culture. On the ninth day when heart failure was first noted, she was given intravenous chloramphenicol and intramuscular procaine penicillin for 3 days, then chloramphenicol and sulfisoxazole in combination for 4 days. Then she was given chloramphenicol alone for 1 day, making a total of 8 days of chloramphenicol therapy at a dosage of 44 mg. per kilogram of body weight per day in divided doses at 6-hour intervals. The child did not respond. On the fifteenth day of illness, she was malnourished. She bled from the cut-down site and from the sites of intramuscular injections. The dose of chloramphenicol was reduced to 18 mg. per kilogram per day. On the sixteenth day of illness, she had gastrointestinal bleeding, hemoptysis, and petechial hemorrhages into the skin. The platelet count was 85,000 per cubic millimeter, the red cell count dropped from 4.0 million to 2.8 million per cubic millimeter, and the hemoglobin dropped from 12.1 Gm. to 8.6 Gm. per cent. The white cell count still showed a shift to the left with a total count of 18,050 and a differential of 96 per cent neutrophils and 4 per cent lymphocytes. Moniliasis was noted on the thirteenth day of illness. *Candida albicans* were found in the mouth and stool. On the eighteenth day of illness, though seriously ill, all antibacterial drugs were discontinued for 18 days. She was given blood transfusions, vitamin K, and gamma globulin. She developed urinary infection, skin abscesses, and sepsis due to *Micrococcus pyogenes* var. *aureus*. After the thirty-seventh day of illness, she was given various combinations of antibacterial agents, erythromycin, bacitracin intramuscularly, penicillin, Furadantin, and streptomycin, but to no avail. The platelet count decreased to 13,000 cubic millimeters, and the hemoglobin dropped to 5.3 Gm. per cent two days before death. Bone marrow examinations were done twice, on the twenty-seventh and thirty-seventh days of illness. The first examination was normal, and the second showed nonspecific changes such as seen in chronic infection, with a moderate increase in histiocytes and esosinophils. The granulocyte series was normal. On the sixtieth day of the illness, the white cell count was 13,800 per cubic millimeter, with 85 per cent neutrophils, 4 per cent lymphocytes, and 11 per cent monocytes. On the sixty-fourth day of illness, the white cell count dropped to 7,000 per cubic millimeter and on the sixty-sixth day of illness to 4,100 per cubic millimeter. No differential was done on these two occasions. She died 78 days after the onset of the illness. Autopsy revealed bronchopneumonia with septicopyemic abscesses due to *Micrococcus pyogenes* var. *aureus* in all internal organs.

SIDE EFFECTS AND TOXICITY

Nine of the 107 patients developed thrombophlebitis. One was in a patient who was given diluted "Chloramphenicol Solution." In two patients other antibacterial drugs, penicillin and sulfisoxazole, were given simultaneously with chloramphenicol in the same vein. Thrombophlebitis developed in 6 patients who were apparently given the drug as recommended. The duration of intravenous chloramphenicol therapy in these cases ranged from 3 to 5 days. The thrombophlebitis started

within 1 to 5 days of initiation of therapy and lasted for 3 to 13 days. In each instance it was treated with warm compresses. No other untoward effect was traceable to this reaction.

Four of the 107 patients developed diarrhea while receiving intravenous chloramphenicol alone. Five more developed diarrhea only after the drug was given orally. Five appeared to be related to an overgrowth of nonsusceptible organisms such as *Proteus mirabilis* (1 case) and *Pseudomonas aeruginosa* (4 cases). Treatment consisted of either discontinuing chloramphenicol or giving another antibacterial agent. In none was it more than a mild temporary disturbance.

Only 1 patient developed a fine, macular skin rash. It appeared on the third day of therapy on the face, neck, and in the groin and was present for only one day. Elixir diphenhydramine hydrochloride was given with prompt relief, although chloramphenicol was continued for 9 days.

Three patients developed hematologic changes, but their relation to chloramphenicol is not clear. A 6-year-old girl died with bronchopneumonia and multiple abscesses due to *Micrococcus pyogenes* var. *aureus*. She developed thrombocytopenia and anemia. Details of this case were discussed previously (Table II). The second was a 19-month-old boy with *Hemophilus influenzae meningitis*. He was given intravenous chloramphenicol in a dosage of 127 mg. per kilogram of body weight per day divided into 2 doses per day at 12-hour intervals for 2½ days. He had an excellent clinical and bacteriologic response. However, 36 hours after discontinuing the drug the white cell count dropped from 15,000 to 5,150 per cubic millimeter, and the granulocytes dropped from 62 to 31 per cent. Fifteen days later the white cell count was 2,300 per cubic millimeter, with 34 per cent neutrophils, 44 per cent lymphocytes, 17 per cent monocytes, and others amounting to 5 per cent. The bone marrow, hemoglobin, red blood cell count, and platelet count were normal. The child was otherwise clinically well. The child was signed out against advice and no follow-up has been possible. The only other medication the child had received was 2 gr. of aspirin twice during the first day of hospitalization.

The third case was that of a 21-month-old girl who was ill for 5 days before admission. She had severe lobar pneumonia with encephalitis, myocarditis, and left pleural effusion. Beginning on the sixth day of illness, she received 70 mg. per kilogram of body weight per day of intravenous chloramphenicol in 4 equally divided doses for 4 days. The white cell count was relatively low before start of chloramphenicol therapy; 5,500 per cubic millimeter, with 73 per cent neutrophils, 24 per cent lymphocytes, and 3 per cent monocytes. She was given two transfusions of whole blood on the sixth and another on the seventh day of illness. On the eighth day of the illness, the white cell count was 2,400 per cubic millimeter, with 38 per cent neutrophils, 57 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils. On the ninth day of the illness without discontinuing chloramphenicol, the white cell count was 4,800 per cubic millimeter, with 33 per cent neutrophils, 58 per cent lymphocytes, and 9 per cent monocytes. She was given another whole blood transfusion on the

tenth day. On the thirteenth day of illness, the white cell count and differential were normal. The red cell count, hemoglobin, and platelet count were never depressed. In addition to chloramphenicol she was given 2 gr. of aspirin 3 times in the first 2 days, penicillin for 1 day, and streptomycin for 13 days.

There were no other side effects or toxicity. In particular there was no fall in blood pressure and no abnormal neurologic manifestations.

DISCUSSION

When oral administration is not possible, intravenous administration of chloramphenicol is practical. The drug appears to be at least as effective when given in this manner as when given orally. The intravenous route should be discontinued in favor of the oral when the patient's condition permits. The recommended dose of intravenous chloramphenicol for infants and children is 15 to 20 mg. per kilogram of body weight every 6 hours (60 to 80 mg. per kilogram of body weight per day).[1, 6] Other studies[1] indicate that this dosage provides blood levels therapeutically adequate for treating seriously ill children with susceptible infections.

In our series of 43 patients with *Hemophilis influenzae* meningitis, 29 received chloramphenicol alone. All of these recovered. Fourteen received chloramphenicol with other antibiotics. Of these, 3 died. These 3 patients received chloramphenicol for 36 hours or less. Two received chloramphenicol for the first time 3 weeks after the onset of the disease. One died 12 hours and the second 36 hours after chloramphenicol was started. The course of the third patient was remarkable in that he was ill for only 7 hours and yet was moribund on admission. The patient was given penicillin, streptomycin, and chloramphenicol but died within 5 hours after admission.

Response to treatment with chloramphenicol in other seriously ill patients infected with susceptible organisms was subjectively impressive, but no objective evaluation is attempted other than to describe the cases briefly.

Blood dyscrasia (aplastic anemia, thrombocytopenic purpura, granulocytopenia, and pancytopenia) has been reported with the use of chloramphenicol.[6-10] In this study two patients developed transient granulocytopenia. Either or both of these may have been due to the infection itself as well as to the chloramphenicol. One patient who developed thrombocytopenic purpura was very sick before being treated. She also received other antibacterial agents, a sulfonamide, aspirin, and barbiturates. She also developed serious complications, namely, cardiac failure, urinary infection, multiple abscesses, septicemia, and moniliasis. It is particularly difficult to assess the role of chloramphenicol in the hematologic disturbance of such a case.

The most common complication clearly due to intravenous chloramphenicol was thrombophlebitis. It developed in 6 cases and responded well in each instance to warm compresses.

SUMMARY

One hundred and seven seriously ill pediatric patients were treated with intravenous chloramphenicol. The clinical responses were evaluated in 91. Sixteen others were included for study of tolerance, side effects, and toxicity.

These 16 had illnesses that could not be expected to be influenced by the drug. In the majority treatment was continued with oral chloramphenicol as soon as the patient's condition permitted. A few also received the drug intramuscularly. Of the 91 patients, 76 improved and 15 did not respond to chloramphenicol. Of the latter, 7 died. These were discussed in some detail.

The average duration of fever after the start of intravenous chloramphenicol in the improved patients was 3 days. The average dosage of intravenous chloramphenicol was 68 mg. per kilogram of body weight per day given in divided doses. To the majority it was given every 6 hours. The average total duration of intravenous administration was 3 days. The currently recommended intravenous dose is 15 to 20 mg. per kilogram of body weight every 6 hours (or 60 to 80 mg. per kilogram of body weight per day).

Except for one patient, the side reactions and toxic reactions were mild and transient. The most common was thrombophlebitis. To minimize this, special care must be exercised in preparation of the "Chloramphenicol Solution" for intravenous use. This procedure is described with emphasis upon the important details. Diarrhea, skin rash, and transient granulocytopenia also occurred in a few cases. One child already critically ill and malnourished developed thrombocytopenia and anemia. This patient also received other drugs, some of which we have been reported to cause similar reactions. At autopsy, abscesses due to *Micrococcus pyogenes* var. *aureus* were found in all the internal organs. The role of the infection itself in causing bone marrow depression in such a case is difficult to evaluate.

It apears that intravenous chloramphenicol is therapeutically effective in infections in which there are indications for this drug. It is relatively very well tolerated and is an important addition to the therapeutic regimen in seriously ill patients until such time that the drug can be taken orally.

We are indebted to Parke, Davis & Company, Detroit, Mich., for generous supplies of "Chloromycetin Solution."

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ERYTHROBLASTOSIS FETALIS CAUSED BY SENSITIZATION TO FACTOR $rh^w(C^w)$

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THE rare blood factor $rh^w(C^w)$ was found in 1945 by Callender, Race, and Paycock[1] as a result of the investigation of a hemolytic transfusion reaction. The first instance of erythroblastosis fetalis attributable to this factor was reported by Lawler and van Loghem[2] in 1947. Since then a number of additional case reports have appeared in the literature. Inasmuch as the incidence of factor $rh^w(C^w)$ is low (5 per cent in Caucasoids and none in Negroes and Chinese[3]) and since this factor is not looked for routinely because of scarcity of antiserum of satisfactory potency, it is felt that instances of sensitization to the factor should be recorded.

CASE REPORT

J. F., a white 36-year-old para vi, gravida vii, was admitted to the obstetric service of Lenox Hill Hospital on Nov. 9, 1957. This was her seventh pregnancy. Her first child had died a few hours after birth as a result of trauma. There were five living children. None had shown jaundice at birth, but on questioning we learned that the fifth and sixth child were anemic and "sickly" during their first two or three years.

In 1955 she underwent a cholecystectomy, and during the operation received a blood transfusion with no reaction. An attempt to locate the donor was unsuccessful. She has not received any blood since then.

On November 12 she spontaneously delivered an apparently normal child weighing 6 pounds, 9 ounces.

The mother's blood type was reported as O, Rh_1Rh_2 (CDe/eDE). The cord blood of the baby was found to be group O, type Rh_1 (CDe/ede), and the direct antiglobulin test was strongly positive. (This test is routinely performed on the cord blood of every newborn infant at this hospital.)

Results of the antiglobulin test were promptly reported to the obstetrical and pediatric services, and fresh speci-

TABLE I*

BLOOD OF	O-A-B GROUP	M-N TYPE	KELL TYPE	P TYPE	DUFFY TYPE	Rh-Hr TYPE
Father	O	N				$Rh_1{}^wrh$ (C^wDe/ede)
Mother	O	M	K	P	Fy^a	Rh_1Rh_2 (CDe/eDE)
Baby	O	MN	K	P	Fy^a	$Rh_1{}^wRh_1$ (C^wDe/CDe)

The mother's serum contained an rh^w antibody with titers:

agglutination method = positive 2 units;
antiglobulin method = positive 44 units.

The incompatible donor selected among 50 prospective donors belonged to group O, MN, $Rh_1{}^wrh$ (C^wDe/ede).

*Dr. A. S. Wiener performed the tests on the blood samples.

From the Blood Bank of Lenox Hill Hospital.

mens of blood of both mother and baby were requested for further study. A specimen of the father's blood was also made available promptly. Tests of the mother's serum were carried out against cells of the father, the baby,

TABLE II

BLOOD OF	GROUP	Rh_o (D)	rh′ (C)	rh″ (E)	rh^w (Cw)	hr′ (c)	hr″ (e)	Rh-hr TYPE
Father	O	+	+	−	+	+	+	Rh_1^wrh (CwDe/ede)
Mother	O	+	+	+	−	+	+	Rh_1Rh_2 (CDe/cDE)
Child 2	O	+	+	−	−	+	+	Rh_1rh (CDe/ede)
Child 3	O	+	+	−	+	+	+	Rh_1^wrh (CwDe/ede)
Child 4	O	+	+	−	−	−	+	Rh_1Rh_1 (CDe/CDe)
Child 5	O	+	+	−	+	−	+	$Rh_1^wRh_1$ (CwDe/CDe)
Child 6	O	+	+	−	+	−	+	$Rh_1^wRh_1$ (CwDe/CDe)
Child 7	O	+	+	−	+	+	+	Rh_1^wrh (CwDe/ede)

TABLE III

DAY	HEMOGLOBIN (GM. PER 100 C.C.)	RED BLOOD CELL COUNT (× 1 MILLION)	RETICULOCYTE (PER CENT)	BILIRUBIN		DIRECT ANTIGLOBULIN	TRANSFUSED	CLINICAL NOTES
				DIRECT	TOTAL			
1	12.2	3.62		0.8	4.3	3+		Hematocrit 25; slight jaundice and pallor
2 A.M.	10.7	2.82	3.8	1.1	4.4			Slightly more jaundiced and pale
P.M.	11.3	3.46						Spleen moderately enlarged
3 A.M.	11.6	2.88		1.1	4.4			
P.M.	11.9	3.00		0.7	3.9			
4	9.4	2.41		0.7	4.1			
5	8.8	2.40		0.7	4.1		80 c.c.	Infant very pale; hemoglobin dropping
6	12.8	3.98						
7	11.3		3.7					
8	10.9	3.21	2.4					
9						Weekly positive		
10	10.9	3.26						
11	10.0	3.64						
12	8.5	2.85						
13							80 c.c.	
14	12.1	4.40						
15	11.2							Discharged
43	7.3	2.72	0.9			Negative	80 c.c.	Readmitted for transfusion
58	10.9	3.05						

and a panel of cells of known groups. There was strong agglutination of the father's and the baby's cells and none with any of the cells from the panel. The serum was then tested against samples of fifty group O, Rh positive bloods (in Blood Transfusion Association laboratories) and only one specimen showed agglutination. As will be seen in Table I, father, mother, and baby were group O, Rh positive.

We then submitted the specimen to Dr. A. S. Wiener for further study. He confirmed our results and identified the factor involved as $rh^w(C^w)$. With the cooperation of the pediatric service, blood samples of the siblings were obtained and tested in Dr. Wiener's and in our own laboratory. The results were the same in both and are listed in Table II. The baby was reported to be slightly jaundiced and not too pale at birth. Because of a progressive anemia, the child was given two transfusions of whole blood during his stay in the hospital. The baby was discharged on the fifteenth day, but was readmitted for a third transfusion a month later. The clinical course is charted in Table III.

DISCUSSION

The case reported here presents a number of interesting features worthy of discussion. We were confronted with a seventh child of the same blood group and apparently the same Rh type as both parents, yet the baby's cells gave a strongly positive direct antiglobulin test. But for this latter finding, this child might not have been followed as closely nor the sensitization to a rare factor been discovered.

We believe that our routine procedure of testing cord bloods of all newborn infants proves its value in this instance. It is our feeling, borne out in a number of instances that have come to our attention, that not enough significance is attached to the finding of a positive antiglobulin test in the absence of classical clinical signs of erythroblastosis fetalis.

Often, the principal indication for exchange transfusion is an elevated serum bilirubin and/or clinical jaundice. Many of these infants require multiple transfusions, each with its usual risks, and have a prolonged hospital stay. A positive direct antiglobulin test on cord blood, demonstration of an antibody in the mother's serum reacting with the cells of the baby and the father (when available), and a moderate anemia on the first or second day may also be considered indication for an exchange transfusion. The baby in this instance showed an anemia on its twenty-eighth day, despite the two small transfusions which had been administered, so that a third transfusion had to be given. Allen and Diamond[4] list anemia as a "conservative indication for exchange transfusion."

SUMMARY

A case of erythroblastosis fetalis caused by sensitization to the rare factor $rh^w(C^w)$ in a seventh child is presented. This factor was present in the blood of the father and the third, fifth, and sixth child born to the mother, and to the seventh child discussed in this report. The significance of a positive direct antiglobulin test on cord blood and the value of routinely performing this test on blood of all newborn infants is emphasized.

I wish to thank Dr. A. F. Anderson, Dr. Irwin P. Sobel, and Dr. J. C. Kilroe for their kind cooperation, Dr. A. S. Wiener for his collaboration, and Muriel Lerch for technical assistance.

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Voodoo Dolls Have Hex

An attractive voodoo doll, imported from Haiti, has recently caused concern because of its toxic properties. The head of the doll is a cashew nut, the shell of which has been carved to form a face. As a result of cutting into the shell, the cashew nut oil seeps onto the shell's surface and its phenol-quality can cause a severe contact dermatitis.

In addition, the eyes of this doll are extremely toxic jequirity beans. These beans, which are seeds of the tropical plant *Abrus precatorius L.*, contain the toxic albumin, abrin. Although, because of its hard coat, the whole seed may be swallowed with impunity, ingestion of the chewed bean produces a clinical picture which is similar to, but more severe than, castor bean poisoning.

Various reports of the toxicity of the seed list one-half a chewed seed as capable of causing symptoms of poisoning and one chewed seed as capable of causing death in man. Since abrin is slowly absorbed from the gastrointestinal tract, a delay of one to three days following ingestion occurs before onset of marked vomiting and diarrhea, which may lead to collapse and death. Treatment includes immediate emptying of the stomach following ingestion, and supportive and symptomatic measures directed toward maintenance of hydration and circulation.

Quantities of such voodoo dolls were imported from Haiti in the form of mixed-drink stirring rods—each cashew nut head being mounted on a 6-inch wooden stirring rod. More recently, cashew nut heads were found being used as decorations on children's straw slippers. We have reports of these stirring rods and slippers being sold in Atlanta, Cincinnati, and Washington, D. C. Undoubtedly they have been sold in other areas in the U.S.A.

Importation of these dolls has supposedly been halted.

From the National Clearinghouse for Poison Control Centers of the U. S. Public Health Service, January, 1959, communication to poison control centers.

PRIMARY FIBROSARCOMA OF THE LUNG IN A YOUNG CHILD

A Case Treated by Lobectomy and Cobalt Therapy

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PRIMARY fibrosarcoma of the lung, in general, is a relatively rare condition. The occurrence of such a lesion in a child under 3 years of age is still more unusual. Review of the literature revealed one possible case by Rosenblum and Gasul.[1] They reported a case of primary sarcoma of the lung in a 29-month-old child. Whether this was a fibrosarcoma or some other type of lesion was not stated.

Because of the extreme rarity of this condition and the lack of response to early lobectomy and cobalt 60 therapy, we are prompted to report this case.

CASE REPORT

L. T., case 41086, a 2-year-9-month-old white boy, was first seen at the U.S. Naval Hospital, Corona, Calif., on Feb. 27, 1956. The history revealed that ten days prior to admission the child had a skin lesion on the ankles and feet which appeared to be due to insect bites. The patient was treated by his local physician with vitamin K, vitamin C, and elixir of Benadryl. In spite of the treatment the rash spread up the legs. The rash was present on the buttocks the next day and the lesion was described as "large, red welts" which on the following day became black and blue. Five days prior to admission the patient developed a temperature of 104° F. rectally. The fever occurred at the same time that the black and blue blotches were noted. The patient was seen at Fort McArthur, San Pedro, Calif., and given terramycin. The fever subsided in two days. The patient seemed to be restless at night and his appetite was poor. Three days prior to admission the parents noted that the child seemed to be having some difficulty breathing. He had also complained of pain in both feet. He was seen at Fort McArthur and because of the history of dyspnea, an x-ray of the chest was taken. The x-ray is said to have revealed a "cannon ball" lesion in the right chest. The patient was referred to the Corona Naval Hospital for treatment of the pulmonary lesion.

Family history and developmental history were normal.

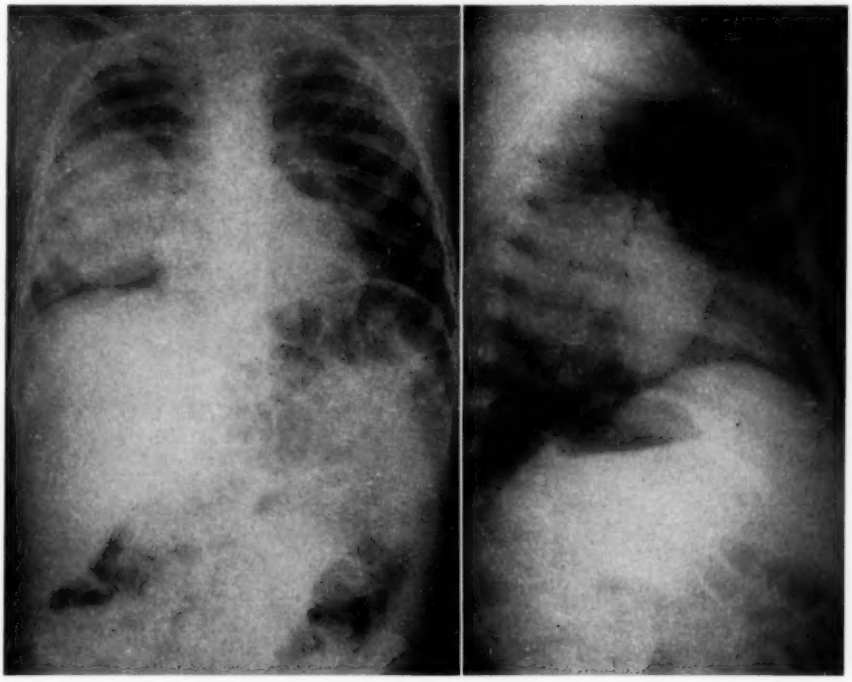
The physical examination revealed a well-developed, well-nourished child who appeared to be about 3 years of age. He was not in acute distress but did have a minimal expiratory grunt. He was 37 inches tall. Weight was 35 pounds. Temperature was 102.2° F. rectally. Blood pressure was 100/40. Physical examination was entirely normal except for the following: There was minimal ecchymoses of the left upper eyelid. Small, shotty lymph nodes were noted in both axilla. These were nontender. The skin on the legs, buttocks, and arms showed numerous petechiae and

From the Department of Surgery, Alexander Blain Hospital, Detroit, Mich.; U. S. Naval Hospital, Chelsea, Mass.; and Department of Radiology, Carobil Hospital, Norwalk, Calif.

fresh and old purpuric spots. There was a swelling and tenderness of the right testicle and spermatic cord, and ecchymoses of the overlying scrotal tissue.

Laboratory findings were as follows: Three complete blood counts were normal as well as platelet counts which ranged from 352,000 to 374,000. The bleeding time was 2 minutes and the Lee-White coagulation time was normal. A throat culture showed normal flora, and a blood culture was negative. A blood urea nitrogen on March 1 was 14.75 mg. per cent. Two urine analyses were normal. Bone marrow studies were normal.

X-rays of the chest taken on Feb. 24 and 29, 1956, showed a well-defined, circular, homogeneous density in the lower half of the right lung field which measured approximately 6 cm. in diameter. The borders were fairly sharply outlined, and the mass was seen in its entirety in the right lower lobe. It was not connected to the diaphragm or to the posterior chest wall. The right minor fissure and the lower portion of the major fissure were also seen as slightly accentuated lines, and there was no evidence of atelectasis of the middle lobe. There was no evidence of compression of the surrounding pulmonary tissue nor was there any displacement of the cardiac or mediastinal structures (Fig. 1). X-rays of the skull and long bones and an intravenous pyelogram were normal.



A. *B.*

Fig. 1.—*A*, Preoperative posteroanterior roentgenogram of the chest illustrating a large mass occupying about one-half of the right hemithorax. *B*, Lateral view showing the tumor to occupy the right lower lobe.

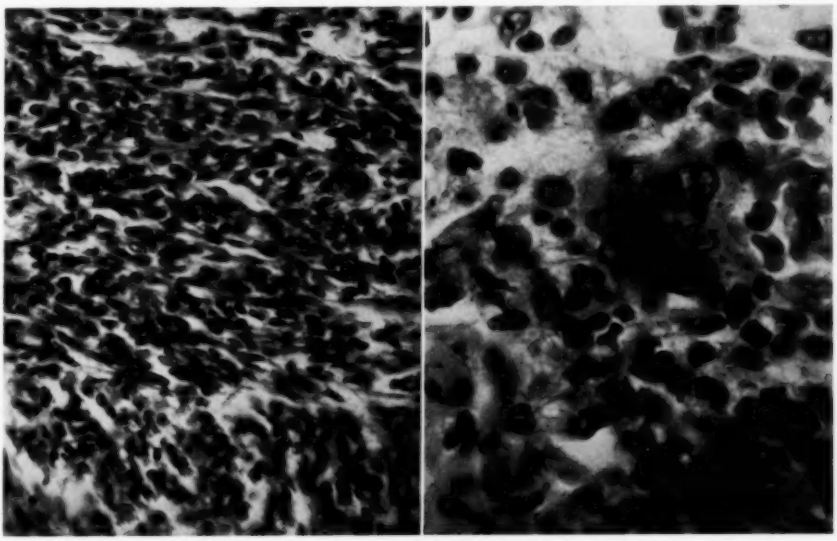
On March 1, 1956, the patient was afebrile and the purpura appeared to be more coalescent and seemed to be less extensive. The testicle on the right was definitely swollen, but there was less swelling of the cord. A urological consultant saw the patient and felt that the testicular swellings were most likely due to the purpuric processes. The patient was seen by a thoracic surgeon (F. S. G.), who noted that there were decreased breath sounds and dullness over the right lower lung field both anteriorly and posteriorly. Nontender, bilateral, small cervical nodes were also noted. The liver was found to be one fingerbreadth below the right costal margin, but the spleen was not palpable. It was the opinion of the surgeon that this was a primary neoplasm of the lung or a large fluid-filled cyst.

Exploratory thoracotomy was recommended after the purpuric rash had cleared. During the next two days the purpura did fade. The swelling in the right testicle also decreased. One week following admission, the purpuric spots had practically disappeared. However, on the following day they recurred. A Rumpel-Leede test at this date was negative. The child was given antibiotics and vitamin K, and two days later the rash had practically disappeared.

It was decided that thoracotomy should be performed. On March 9 the patient was taken to the operating room and a right parascapular incision made. The fifth interspace was incised. The pleural space was partially obliterated by rather firm adhesions between the superior dorsal segment of the right lower lobe and the parietal pleura. These adhesions were divided. A large mass was noted occupying more than half of the right lower lobe. This mass was completely confined to the right lower lobe and was of firm consistency. The lymph nodes in the hilar area were somewhat larger than normal and had a brownish hue. The pulmonary artery going to the right lower lobe was isolated in the major fissure and the segmental branches ligated and divided. The inferior pulmonary vein was isolated, ligated, and divided. The bronchus to the lower lobe was readily located. The superior dorsal segmental bronchus was isolated and divided and its stump sutured with interrupted 4-0 silk sutures. The lower lobe bronchus distal to the superior dorsal segmental bronchus was then divided and its stump reapproximated with interrupted 4-0 silk sutures. A penicillin and streptomycin solution was placed in the pleural space and a thoracotomy tube connected to water-sealed drainage. The wound was then closed.

The pathological report was as follows: "The specimen consists of the right lower lobe of the lung. Occupying the major portion of the structure is a tumor mass 6 cm. in diameter, the cut surface of which bulges. It is, for the most part, fairly soft, uniform gray, and resembles lymphoid tissue. The borders of the tumor are sharply circumscribed and there appears to be a fibrous capsule about it. The surrounding lung is collapsed. There is no invasion of the bronchi or veins. Portions of the tumor are hemorrhagic and necrotic. A small bronchial lymph node 8 mm. in diameter is not invaded by tumor. The microscopic sections revealed the tumor to be composed of solid masses of cells resembling embryonic mesenchyme. In some areas these cells are stellate and widely spaced, while in others they are condensed into sheets and nodular masses of closely packed spindle cells seen to project into the lumen of these vascular spaces and in many instances there appears to be no endothelium separating the lumen from the tumor cells. Mitoses are quite frequent. In the sections examined, there is no differentiation of these cells toward muscle, cartilage or epithelium. Frequently there are vacuolated cells containing lipoid droplets. The surrounding lung is compressed apparently by expansion of the tumor,

there is a zone of reactive fibrosis forming a capsule about the tumor. Toward the hilum the capsule is penetrated microscopically by masses of tumor cells. Two bronchial lymph nodes present in the sections are not involved by tumor. The final diagnosis was undifferentiated mesenchymal sarcoma, which suggested its designation as an anaplastic fibrosarcoma" (Fig. 2).



A. *B.*

Fig. 2.—*A* and *B*, Photomicrographs of the fibrosarcoma of the lung. *A*, demonstrates the spindle-shaped cells closely packed in sheets and having a mesenchymal appearance (×400). *B*, illustrates, under higher power, that the cells are pleomorphic and anaplastic with little cytoplasm (×1,060; reduction 3/7).

These slides as well as a portion of the tumor mass were sent to the Armed Forces Institute of Pathology, which concurred in this opinion.

The patient's postoperative course was uneventful. On the second postoperative day it was noted that his purpuric rash had practically disappeared. On the sixth postoperative day the patient was discharged from the hospital in very good condition. Five days after leaving the hospital the patient was seen in the outpatient clinic. The patient's parents said that the boy had been sleeping much more soundly and was breathing with no difficulty. He was able to elevate both arms above his head without any distress. There was no cough. Examination of the patient at this time revealed only a slight decrease of breath sounds over the right lower chest. Several small areas of petechiae were noted on the flexure surface of the left knee and also on the scrotum.

On March 26, eleven days after discharge from the hospital, the child had no complaints. He weighed 36 pounds. He was very active about the house and had a good appetite. Physical examination was essentially negative. Laboratory studies on this date showed a blood urea nitrogen of 20.25 mg. per cent, total protein 6.85 mg. per cent, albumin 5.1 Gm. per cent, and globulin 1.75 Gm. per cent. A complete blood count, sedimentation rate, hematocrit, and urinalysis were done and these were all normal. An adequate platelet count was again noted in the blood smear.

On April 9 the patient seemed to be tiring a little more easily. However, physical examination was entirely normal. X-rays of skull, long bones, and chest were taken and these were interpreted as normal.

On August 7, 1956, the patient was seen in the outpatient department where the parents stated that the boy had developed a cough which had not subsided with terramycin which had been given by his local physician. X-rays of the chest were taken at that time and it was noted that there was a large hilar node and a questionable infiltrate in the right upper lobe parenchyma. The child had not lost weight and had developed no dyspnea. He did not complain of any chest pain.

The patient was admitted to the Letterman Army Hospital (case 4243-050) on August 14, 1956. The temperature was 100.4° F. Weight was 37 pounds. Blood pressure was 108/62. He was found to be a well-developed, well-nourished blond child in no distress. A firm ½ by ½ cm. node was palpated in each supraclavicular area. Chest expansion was equal, and the lungs were clear and resonant with no râles audible. There were no nodular masses along the incision. The rest of the physical examination was essentially normal.

Laboratory findings at this time revealed a white blood count to be 3,600, neutrophils 29, lymphocytes 48, monocytes 15, eosinophils 5, and basophils 3. Hemoglobin was 12.5 Gm. Bleeding and coagulation times were normal. Hematocrit was 38 per cent. Repeat white blood cell counts varied from 5,000 to 10,000, and the differential counts also showed considerable variation. Urine analysis was negative. On Aug. 28, 1956, a right supraclavicular node biopsy was performed. No tumor cells were found in these nodes. Cultures from these nodes were also negative. On September 11 a bone survey, including skull and chest x-rays, was normal except for a minimal soft tissue density in the right lower posterior lung field.

On September 13 a right thoracotomy was performed. Tumor tissue was found in the parietal pleura along the line of the previous incision. The hilum was infiltrated with tumor tissue, most of which appeared to be encapsulated by a thin, bluish-white membrane. It was realized that there was massive involvement of the mediastinum and that nothing surgical could be done which would be of benefit to the child. Therefore, the chest was closed after a thoracotomy tube had been placed. The child recovered and was discharged from the hospital one week after the operation.

He was referred to another hospital for radiation therapy. He was given cobalt 60 at a distance of 75 cm. through 4 portals. Therapy was begun on September 27 and completed on November 29. Each field was treated to completion and then the next was started. Thus, portal 1 (AP mediastinum) was treated daily up to 3,900 r. (skin), then 2 (right PA 45 degrees) was started and 680 r. given. Following this, 3 (right PA chest) and 4 (right AP chest) were instituted and 3,000 r. and 3,200 r., respectively, administered. Approximately 200 r. skin dose was given at each treatment which was daily, except Saturday and Sunday. The total tumor doses were 3,247 r. to the mediastinum and 4,462 r. to the right lung. The fields were stationary, and measured as follows: portal 1 was 6 by 15 cm., portal 2, 2 by 15 cm., portal 3, 10 by 13 cm., and portal 4, 10 by 12 cm. On Jan. 10, 1957, he received a skin dose of 100 r. and a tumor dose of 75 r. to the AP right chest through a field of 12 by 15 cm. The following day a skin dose of 50 r. and a tumor dose of 38 r. to the AP left chest through a field of 8 by 15 cm. was given. This therapy did produce a slight decrease in the size of the metastatic nodules.

On January 6 the boy was readmitted to the hospital because of lethargy, anorexia, and cough. Following x-rays, he was found to have a massive pleural effusion on the right lung and numerous spherical nodules in the left lung.

Laboratory examination at this time revealed a normal urine analysis and a hemoglobin of 10.5 Gm. The white blood count was 12,150 with 88 per cent neutrophils and 8 per cent lymphocytes. He was treated with radiation, terramycin, thoracentesis, plus Meticorten and improved enough to return home on January 18. However, he still remained somewhat lethargic and had his chronic cough.

His final admission to the hospital was on February 8 because of dyspnea. Physical examination revealed an acutely ill boy in marked respiratory distress. Respirations were 100 per minute. He had a harsh cough productive of a small amount of pinkish sputum. There was only slight movement of the right thoracic cage. The entire right chest was dull with absent breath sounds. Harsh breath sounds were audible over the left lung. Laboratory data at this time revealed a hemoglobin of 10.5 Gm. The white blood count was 2,800, with 66 per cent polymorphonuclear cells, 30 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. A roentgenogram of the chest revealed the right side to be completely opacified, a finding consistent with the presence of large amounts of fluid (Fig. 3). The metastatic nodules appeared to have increased slightly in size on the left side. Thoracentesis was attempted the day after admission, but no fluid was obtained. Then it was felt that this opacity seen on the x-ray was consolidated lung probably replaced by tumor tissue and not fluid. He was treated with antibiotics and morphia as indicated. He died on March 10, 1957.

Fig. 3.—Posteroanterior roentgenogram of the chest approximately one year after surgery and one month before death. The right hemithorax is completely opacified. There are numerous metastatic nodules throughout the left lung.

Autopsy showed an extensive tumor in the right lung and pleural cavity with extension of the tumor to the diaphragm and to the liver. There were multiple metastatic nodules in

the left lung but none elsewhere. There was atelectasis of the left lower lobe. Mild chronic passive congestion of the lungs and liver was noted. An emphysematous bleb was noted in the left lower lobe.

The microscopic examination of the tumor tissue from the autopsy specimens were the same as that seen in the previous sections of the tumor removed surgically, that is, anaplastic fibrosarcoma of the lung.

DISCUSSION

It is difficult to determine the incidence of fibrosarcoma of the lung since little attempt has been made, until the past ten years, to classify these tumors other than as bronchogenic sarcoma of the lung. Furthermore, the number of fibrosarcomas reported are too few to be of any statistical significance. Stout,[2] in 1948, emphasized that the use of terms such as "neurogenic sarcoma" and "spindle cell sarcoma" were meaningless, that they were causing a great deal of confusion, and that they should be abandoned. Since then, more specific classifications of sarcomas of the lung have been made and have thus helped to clarify the literature on this subject.[3]

Primary bronchopulmonary fibrosarcoma occurs at all ages. Few cases have been reported in older children, but we have been unable to find any case, other than our own, under 3 years of age.[4-6] These may arise in the larger bronchi or in the lung parenchyma. In our case the tumor arose in the lung parenchyma. Jensik[7] had a 5-year-old patient with an intraluminal bronchial fibrosarcoma at the orifice of the right middle lobe. He performed a right middle and lower lobectomy. The child is well one year postoperatively. Curry and Fuchs[8] reported a case in which the child expectorated a fibrosarcoma of the bronchus and was well with no sign of recurrence four years later. Our patient was not as fortunate.

It is infrequent that one can make an exact cytological diagnosis of such a tumor before surgery. Occasionally bronchial secretions, bronchial, and/or lymph node biopsy have revealed the exact nature of the lesion. Some of the conditions which were considered in the differential diagnosis included hamartoma, postinflammatory "tumor," bronchogenic cyst, fibroma, carcinoma, and other types of sarcoma such as leiomyosarcoma, granuloma, and teratoma. We were unable to make a definite cytological diagnosis preoperatively in this case.

We are unable to assess the value of surgical excision and/or x-ray therapy in this condition from the study of the few cases that have been reported in the literature. The well-differentiated fibrosarcomas appear to have a better prognosis, as would be expected, than the undifferentiated anaplastic type. We feel that surgical excision is mandatory for a number of reasons: (1) Frequently, it is necessary in order to make a definite diagnosis. (2) It offers palliative therapy if nothing else, that is, the dyspnea, cough, hemoptysis, etc., that these patients frequently have are relieved temporarily. (The dyspnea did disappear in our case.) (3) It is the only form of therapy available that offers any hope of cure. Ochsner and his co-workers[9] recently reported a patient with leiomyosarcoma of the lung which he removed in 1936, and the patient is still alive and well. In our case, cobalt therapy

was instituted empirically, for we did not know whether this type of treatment would be of any benefit or not. We realized that, in general, fibrosarcomas are relatively radioresistant to radiation therapy, but we hoped that this case might prove to be the exception. There was a slight decrease in the size of the metastatic nodules following their irradiation, as noted by a roentgen film of the chest, but this was hardly worth mentioning. No subjective improvement occurred. As noted, the patient died thirteen months after the onset of the symptoms despite the methods of therapy instituted.

SUMMARY

Primary fibrosarcoma of the lung in a 2-year-9-month-old child has been reported. This is the youngest case of this type of sarcoma of the lung ever recorded, and the only case recorded in a child treated by lobectomy and cobalt therapy. This was a very anaplastic fibrosarcoma which responded poorly to the above-mentioned therapy. Excision of the lesion relieved the boy's dyspnea temporarily, and the cobalt therapy had little or no therapeutic value. The patient developed extensive metastases and died thirteen months after the onset of symptoms.

We wish to gratefully acknowledge the cooperation of the Armed Forces Institute of Pathology for making available the photomicrographs of the tumor and their assistance in interpreting the nature of the tumor.

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THE PROTEIN REQUIREMENT OF INFANTS

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THE subject which I will discuss is a controversial one among pediatricians. It is also one upon which the Food and Nutrition Board could not agree. In the current edition of *Recommended Dietary Allowances*[1] there appears for the first time in history an empty space rather than a figure for the infant's protein allowance. A reference mark leads one to a note where a somewhat equivocal statement is found. There is disagreement among the nutritionists, among the pediatricians, and among the industrialists who attempt to provide us with the materials to feed our babies. The advocates of high and of low protein are people of integrity and good will, although some are emotionally charged. Perhaps I flatter myself that I can review the subject objectively but I shall at least make the attempt.

To understand the background for the two conflicting points of view, it is necessary to go back a little way into pediatric history. The first good analyses of milk protein came in the '80s at which time the relatively low concentration of protein in human milk was definitely established. Meigs[2] of Philadelphia was the first American to demonstrate this convincingly. It is not surprising that the difference was seized upon by the pediatricians of that day, particularly by Rotch of Boston, as the explanation of why artificially fed infants failed to thrive as well as those fed at the breast—they could not tolerate the protein. Rotch was the father of formula feeding and developed a series of low protein formulas prepared by diluting cow's milk and adding sugar, the dilution gradually decreasing as the child grew older. This was acclaimed by American pediatricians as the truly "scientific" method of infant feeding and was held in high regard during the first two decades of the present century. My father was one of its staunch advocates. By and large it seemed to work well, but from time-to-time there were exceptions which caused concern —experiences like the following which I can recall my father telling me about: A baby from out of town would be put on a Rotch formula and not seen again for some time. Months later would come a letter from the baby's mother saying: Dear Doctor, we tried your formula. The baby got worse and worse. Finally, in despair, we fed him whole milk from the neighbor's cow. He began to pick up at once. I thought you might like to see his picture. Enclosed would be the photograph of a child, the picture of health itself. It was a little upsetting.

Then, about the time of World War I, Osborne and Mendel came on the scene with their classic studies of rats fed diets of pure protein supplemented with amino acids. Proteins were no

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longer just proteins. There were differences in quality. Casein was not as good a protein as lactalbumin and cow's milk protein was not as good as that of breast milk. Mendel appreciated the significance of the work for pediatries, but he was disappointed that so few pediatricians were interested in it. He once told me that he thought there were only two, my father and John Howland, who read his papers. My father, however, was greatly impressed by the work at Yale. It explained his failures with the Rotch formulas; and he had much to do with bringing the new concept to the attention of the pediatricians and medical men in general.[3] More protein had to be fed when giving cow's milk in order to provide the proper amounts of certain amino acids. Exactly how much more was not clear. Double the quantity provided by breast milk seemed not too much. The concept that 15 per cent of the calories should be derived from protein when cow's milk was fed was developed at this time and was supported by observations on the spontaneous intakes of healthy older children. In terms of grams of protein per kilogram, this meant an intake of 3 to 4 Gm. per kilogram as opposed to approximately 2 Gm. provided by breast milk.

Infants on these higher intakes did well; on the whole they did better than on the Rotch formulas; progress had been made. But the difficulties were not altogether solved. Raw milk was still used for routine feeding and not all infants could take the higher protein intake with impunity; some had trouble with curd indigestion. Dilution with thin starch gruels helped, but the real solution was not long in coming. It was processed milk—processed at home or in the dairy. I was a hospital intern in 1921 when the first powdered milk was fed in the Babies' Hospital in New York. All the staff were greatly impressed by the fact that the heat processing had so altered the protein as to permit relatively high intakes with no sign of curd indigestion. Evaporated whole milk was equally successful but there was a prejudice against canned products and they were slow in coming into general use. For some years the majority of babies continued to be fed on fresh milk, and the curd problem had to be solved in other ways, namely, by the application of heat and by treatment of the milk with acid. The practice of terminal sterilization came in in the '20s and the same decade saw the advent of acidified milk, precurdled in fine curds before feeding. There were other virtues claimed for acidified milk by Marriott,[4] but Brenneman[5] showed clearly in 1929 that its benefit was due to its effect in avoiding curd indigestion.

The impetus of the Mendel and Osborne experiments has continued up to the present time. The belief persists that cow's milk protein is substantially inferior in quality to that of breast milk and that considerably more protein must be given to the artificially fed infant in order to obtain comparable results. Nevertheless, within the past two decades a body of evidence has been obtained which indicates that their studies are not quite so applicable to infant feeding as had been thought:

1. Osborne and Mendel, it may be recalled, found that casein was inferior to lactalbumin as regards rat growth and required the addition of cystine to overcome this difference.[6] There seems to be no doubt that

sulfur-amino acids are limiting in rat growth when casein is fed, but the requirements of different animal species are now known to differ. Birds, for example, require arginine in considerable quantity for feather formation. Hairy animals presumably have a high requirement for cystine,[7] hair being rich in this amino acid. The baby, having no need for rapid hair production, is another matter.

2. There is evidence that milk processing as now carried out makes nitrogen more available than was the case when raw milk was fed. Recent investigators find quite regularly that 85 to 90 per cent of the nitrogen of processed cow's milk is absorbed. This contrasts sharply with the experience on raw milk in which substantial amounts of casein were lost in the stools in the form of beanlike curds.[8] Two proprietary milk feedings, designed as partial imitations of breast milk, both of which provided only a little more protein than breast milk but all of it heat processed, have proved clinically successful and are showing sustained and increasing popularity. In a recent study in which premature infants were fed at low protein levels Barness and associates[9] were unable to demonstrate any striking superiority of breast milk protein.

3. Net protein utilization (NPU) values* for a standard cow's milk protein and a standard breast milk protein have recently been determined by Platt[10] under the auspices of UNICEF. The difference is surprisingly small (81.5 for cow's milk and 94.5 for the breast milk). The standard cow's milk was an American skim milk powder, the standard breast milk being a powdered preparation supplied by the Dutch Red Cross. From the figures given, it would appear that the two proprietary cow's milk feedings mentioned above which provide approximately 10 per cent of the calories as protein provide a somewhat greater margin of safety above the protein minimum than does breast milk.

As far as the immediate nutrition of the infant is concerned, it appears that the feedings containing 10 per cent of the calories as protein or 15 per cent of the calories as protein (roughly 2 Gm. and 3 Gm. per kilogram, respectively) are both eminently satisfactory. Both have stood the test of time and clinical differences have not been observed. A theoretical advantage can be claimed for each. The higher protein feeding would appear to provide a greater margin of safety against protein deficiency than the lower protein intake. However, the resulting higher obligatory urinary water required to excrete the additional urea would appear to offer a lesser margin of safety against dehydration. The practical importance of either of these theoretical advantages has not been demonstrated.

From the point of view of health, obvious differences have not been revealed by experience on these two types of diets. Yet it may well be that more detailed study will reveal subtle differences of which we are not now aware. There are reasons for believing that such subtle differences do exist. The evidence for this is much of it indirect and far from conclusive.

*The *NPU value* represents the proportion of ingested protein retained as contrasted with the *biological value* which is defined as the proportion of absorbed protein which is retained. It must be recalled that both NPU values and biological values are significant only under conditions of deficit or at marginal intakes. Once the minimum requirement is exceeded, additional protein fed is deaminated and excreted in the urine as urea and the proportion of retained protein falls regardless of quality.

Nevertheless, it is of some interest to review it and to speculate as to its significance.

It is clear that the nitrogen content of the growing organism can be influenced to a limited extent by the quantity of nitrogen ingested. An excess of nitrogen beyond the minimum requirement level is not *all* excreted as urea; a small fraction of it is retained. The excess retained is not as great as some of the earlier balance studies, such as that of Swanson,[11] would indicate; it appears that some systematic error increased the apparent retention figures. Nevertheless, it is clear from carcass analyses of animals fed low and high protein intakes[12-14] that the nitrogen content of the body is higher on the latter; the body weight is little affected, the increase being largely at the expense of fat. Something is known in regard to the nature and location of this excess nitrogen. Nearly all the tissues show some increase in nitrogen, the largest percentage increase being in the liver, kidneys and adrenals, organs concerned in the degradation of amino acids, in nitrogen excretion, and in gluconeogenesis from protein. A part of the increased nitrogen retention thus represents compensatory hypertrophy of tissues needed to handle the added nitrogen load. There remains, however, some excess nitrogen not so accounted for. Although it is often stated that nitrogen is retained only in the form of organized cellular protein, this is now known to be incorrect. Some of it is present as simple nitrogen compounds in the extracellular fluids as well as in the cells. The level of blood urea depends upon the nitrogen intake.[14a] Infants fed on cow's milk carry distinctly higher urea levels than those fed on breast milk. Considerable amounts of free amino acids have also been demonstrated in tissue cells.[15] Do these nitrogen moieties function as "reserves"? That is the $64,000 question.

Quite apart from diet, the percentage of nitrogen present in the body changes with growth. About 3 per cent of the nonobese adult body consists of nitrogen whereas in the newborn child it is only about 2 per cent and in the premature infant even less. The body of the infant contains a larger proportion of extracellular fluid, a smaller proportion of cells. It seems logical to try and make the infant mature as rapidly as possible, in other words, to turn him from a feeble, vulnerable creature into a tough adult. But can we really do this by feeding him more protein? We can make him gain nitrogen more rapidly and assume the adult 3 per cent level of body composition more rapidly. We can push the composition of his weight gain up to 6 per cent nitrogen without difficulty, but are we really making him more mature? Is he making enzymes better? Or is he just storing up somewhere materials that can be used for synthesis only at a predetermined rate? These are unanswered questions. Cusworth and his co-workers[16] found that the red cells of infants contained considerably more free amino acids than had been found by Stein and Moore[17] in adults. Were these moieties accumulating because they were not being used?

The real answer to the protein intake question is under what regimen does the infant best withstand the challenges to which he is subject—in infancy and perhaps in later life? This is an area in which our knowledge

is very deficient. Infants cannot be challenged, only the results of natural challenges can be recorded. But challenge experiments can be carried out in suitable animals. Many such experiments have been carried out, but many more are needed, for the results are far from clear-cut and are often equivocal. The challenge of infection is one that occasions the most concern. Will a high protein intake confer a measure of protection against infection or, conversely, will a low protein intake impair it? On impulse, one would be tempted to answer in the affirmative and to assume that this had been demonstrated, but when the evidence is examined one is given pause. The literature in experimental animals is conflicting, and there is evidence that the situation varies with different microbial agents. Thus, Dubos and Schaedler,[18] studying infections in the mouse caused by the staphylococcus and the tubercle bacillus, found, as had other workers with the latter organism, that resistance was improved by a generous protein intake. On the other hand, the studies of Sprunt and Flanigan[19] with viral infections (vaccinia, swine influenza and the Rous sarcoma virus) led to just the opposite conclusion; and Schneider and Webster,[20] in exceedingly meticulous experiments, were unable to demonstrate any effect of diet on the resistance of the mouse to *Salmonella enteritidis*. The possibility that enriching the diet may benefit the parasite as well as the host and, in some instances at least may enable the parasite to gain the upper hand, must be considered. There are exceptions to the generalization that a low protein intake improves resistance to a viral invader but decreases it to a bacterial invader. The patient with kwashiorkor appears to show poor resistance to measles but, despite an extensive dermatitis, he rarely suffers from secondary pyogenic infection of the skin.

Data from humans relating infection to diet are far from conclusive. Breast milk has enjoyed a high regard as a prophylactic against infection, but controlled observations that would permit one to attribute this to its low protein content are lacking. Dancis and associates[21] studied the antibody response to DPT vaccination in a group of infants (some of whom received 10 per cent and some 20 per cent of their calories as protein). The numbers were small, not sufficient to detect minor differences, but it is significant that gross differences were not observed.

It is clear that the relation between nutrition and infection is not a simple one. In some of the studies of Sprunt, for example, cyclic changes were noted (an initial drop in resistance as protein was suddenly reduced, a more prolonged phase in which on the depleted diet resistance was greater than normal, and a terminal phase of increased susceptibility). Obviously, we need much more information. The doctrine that dietary enrichment means better health, attractive as it is, must be critically evaluated. It may be well to recall the observations more than a century and a half ago by Underwood[22] and by Jenner[23] that certain infections were associated particularly with well-nourished individuals.

In the case of poisons, too, conflicting results are obtained, depending upon the particular poison in question. For one poison a high protein diet is best; for another a high

carbohydrate or a high fat diet with low protein works better. It is impossible to generalize. We need to have studies with a number of different stresses (dietary stresses, climatic stresses, exercise, and many others). It is also clear that the early nutritional pattern may affect stresses that develop late in life. An excess of one foodstuff may be beneficial or it may lead to the development of compensatory disposal metabolic patterns which continue after the excess has been terminated and lead to untoward results. In the case of calcium, for example, Henry and Kon[24] observed that a high calcium diet given to young rats favored retention in early life but predisposed to osteoporosis in later life. Similar observations were made by Gershoff and associates[25] in dogs. The effect of the protein level in early life upon the stresses of later life needs to be studied in greater detail. The effect of the early dietary pattern on growth is being studied. Interesting observations in rats have been carried out by Widdowson[26] who found that an abundant diet given in the early weeks of life caused a pattern of growth to be indelibly imprinted which resulted in greater ultimate size regardless of the later diet. It is not clear whether it was the higher protein intake or the higher calorie intake which produced the result. Can it be that the increasing stature of Americans is conditioned by a higher protein intake in infancy? We are also faced with the question—Is increasing stature desirable? The bigger individual may have greater physical prowess, but in our present civilization this is not at a premium. Machines are replacing manual labor; we ride instead of walk when we want to go somewhere. With less physical exertion obesity seems to be on the increase, a condition associated with well-known health hazards. The big individual requires more calories to sustain him, but is correspondingly vulnerable to calorie deprivation as was amply demonstrated in concentration camps and among prisoners of war. I shall not attempt further speculation. I wish only to emphasize the great need for study in the field of remote as well as more immediate effects of diet.

In view of our present ignorance, what is the best way to play safe as far as feeding protein to infants is concerned? Are we safer with 2 or with 3 Gm. per kilogram or more? I shall answer that question very simply by saying, I don't know and I don't know of anyone who does know.

I have heard industrial concerns criticized because they try to persuade us what to feed our infants. There is much that I deplore in current sales techniques which often distort or attempt to controvert established truth. On the other hand, I am not troubled by promotional efforts when the facts are as equivocal as they are here. As long as our industrial friends feel the obligation to sponsor fundamental research designed to answer our questions, and as long as they are willing to adapt their products to new knowledge as it comes out, I think we have no occasion to fear. We shall have the final answers that much the sooner.

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ON THE PROTEIN ALLOWANCES FOR YOUNG INFANTS

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AFTER several decades of relative quiescence, controversy has again arisen about the protein allowances for young infants. The chief enigma is this: if normal full-term infants thrive at the breast on estimated intakes of 2.0 Gm. of protein per kilogram of body weight per day, why should the recommended allowance for young infants fed cow's milk mixtures have been stated as 3.5 Gm. in the 1953 revision of the *Recommended Dietary Allowances*[1] compiled by the Food and Nutrition Board of the National Research Council? In the 1958 revision,[2] the column for protein allowances for young infants has neither the 2.0 Gm. which would have suited some pediatric advisors nor the 3.5 Gm. recommendation which would have suited others (including the authors); instead, it refers to a discussion which urges breast feeding and presents briefly the evidence which prevented a firm recommendation to the Committee on Dietary Allowances of the Food and Nutrition Board.

Some of the disagreement arose from a failure to recognize that the primary aim of the *Recommended Dietary Allowances* is to supply ample allowances.[3, 4] They are "designed to maintain good nutrition in healthy persons in the United States under current conditions of living and to cover nearly all variations of requirements for nutrients in the population at large. They are meant to afford a margin of sufficiency above minimal requirements and are therefore planned to provide a buffer against the added needs of various stresses and to make possible other potential improvements of growth and function. . . . They may be more generous than would be practical for feeding large groups under conditions of limited food supply or economic stringency." Naturally these aims derive from the abundance of food in this country. On the other hand, international organizations such as UNICEF, the Food and Agricultural Organization of the United Nations, and the World Health Organization, who try to combat malnutrition in technologically underdeveloped countries with limited funds, are more concerned with "safe practical" or "average minimal" allowances.[5, 6] Since "ample allowance" would appear a more natural guide to infant feeding than "safe practical" or "average minimal" allowance, why was it impossible for a group of American pediatricians to agree on a figure for protein allowances? The answer lies in the inconclusive nature of the evidence, both old and new,

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and a concern about feeding practices which, starting with obesity and calorie overnutrition,[7] has overflowed to animal fats, calcium, and now protein. This paper presents an analysis of data available for making judgments, some obstacles to their interpretation, and conclusions which appear valid to the authors for the current practice of infant feeding.

In discussing protein allowances, one must remember that the protein ingested by young infants is usually in milk, a complex natural food which contains other important nutrients, the intake of which may be made inadequate or excessive as one concentrates on the protein allowance. The expression of the protein allowance as percentage of calories ingested is an attempt to relate the protein to at least the total energy intake. Processing of milk may considerably alter the availability of the protein and other nutrients and thus affect judgment of the adequacy of the milk. For example, less recently scurvy and more recently megaloblastic anemia and convulsions due to pyridoxine deficiency were caused by changes in methods of processing cow's milk.

Three kinds of data which have been used in attempts to formulate protein allowances are: (1) estimates of food intake and progress, usually weight gain, of apparently thriving infants; (2) a theoretical formulation of protein requirements; (3) experimental studies which include determinations of nitrogen balance of infants at different levels of protein or amino acid intake, and studies of animals.

ESTIMATES OF FOOD INTAKE

Survey of Feeding Practices.—Studies of empiric feeding practices combined with chemical analyses of the milk fed gave early estimates of nutritional allowances for thriving infants. In judging their value one must keep in mind the following considerations:

(a) The estimates of protein content and the amount of milk ingested were rough because the number of actual measurements of the latter were few: for breast feeding, measurement of actual intake required weighing the infants before and after many nursings; for artificial feeding with either human or cow's milk, careful weighing of milk containers before and after feedings. Furthermore, the actual chemical analyses of the milk consumed posed a problem, particularly with breast feeding, because of the difficulties in obtaining adequate sampling. This is of less importance with cow's milk since so much of the cow's milk used represents pooled samples from large herds.[8, 9]

(b) The criteria for health may be hard to define. Increase in weight, growth in height, osseous and muscle development, concentration of hemoglobin or of other blood constituents, and incidence of infection have been related to food intake, but even when these parameters have been measured carefully the studies have not been designed to permit a critical answer concerning the importance of variations in protein intake alone.

In spite of these considerations, studies of empiric feeding practices have given useful information. In

the first place they have the advantage of representing the food intakes of infants in a natural habitat, i.e., while being fed and cared for by their mothers. Second, their very lack of precision is a built-in caution against the rigid use of averages which become "tyrannical because of the necessity of their expression as numerical symbols." Actually, the broad adaptive psychologic and physiologic powers of infants have made a shambles of such attempts at tyranny.[10-13]

For breast-fed infants, the relatively small amount of data available did not hinder the Food and Nutrition Board's estimate of the protein allowance as approximately 2.0 Gm. per kilogram per day during the first 6 months of life. The reasons for this are simply stated as follows: "For infants, human milk is the desired source of nutrients. Breast feeding is particularly indicated during the first month of life when infants show handicaps in homeostasis due to different rates of maturation of digestive, excretory and endocrine functions. Protein needs in early infancy are fully met by mother's milk when infants are fed at the breast and the process of lactation in the mother is not limited. For this first period, therefore, breast feeding should be encouraged as the desired and best procedure for meeting nutrient requirements. Although there is variation in protein content of mature breast milk, the average concentration is about 1.2 Gm. of protein per 100 ml. Usual quantities consumed by nursing infants afford an intake of about 2.5 to 1.5 Gm. of protein per kilogram body weight during the first six months of life. The dietary allowances to meet these needs are, therefore, afforded the mother. These are taken into account as additional allowances for the woman during lactation, and are included in the Table of Recommended Dietary Allowances."[2] In other words the protein allowance for a breast-fed infant is met by the dietary allowances, good health, ability and willingness of his mother to nurse him, and by faith in his appetite as a guide to his total milk, and therein included protein intake.

With cow's milk mixtures there is, however, much more room for controversy about the protein allowance as judged from feeding practices. In Fig. 1 is presented, for various feeding mixtures, the distribution of calories derived from protein, fat, and carbohydrate as a percentage of the total calories. Readers are referred to Powers' articles[12, 14] for information, the use of which might prevent our feeding practices from becoming or continuing as inelegant as our antibiotic practices. Cow's milk mixtures modified to resemble human milk in the distribution of calories included the cream and top milk mixtures of Biedert and Meigs, the "percentage" mixtures of Rotch (1893), and butter-flour mixtures of Czerny-Kleinschmidt (1918) (Fig. 1, column 1). Other mixtures which give 9 to 10 per cent of the calories as protein (approximately 15 to 25 per cent more protein than the 7 to 8 per cent in human milk) are presented in column 2 of Fig. 1. They include the whey-adapted milk of Schloss, the artificial mother-milk of Freudenthal, the synthetic milk adapted of Gerstenberger and Ruh

(1919), and other proprietary preparations used in this country. The butter-flour mixtures of Moro (1920) supplied 10 per cent of the calories from milk protein and an additional 1 or 2 per cent from the protein of the flour. Sweetened condensed milk, column 3, also supplies 10 per cent of the calories as protein. Marfan[15] used a concentrated half-skimmed cow's milk to which sugar had been added, and the distribution of calories, column 6a, is virtually the same as that of sweetened condensed milk.

As already stated, the majority of cow's milk feeding mixtures currently in use supply approximately 15 per cent (13 to 16 per cent) of the calories as protein (column 4). It is difficult to determine the origin of the rule of thumb used some 60 years ago by Budin,[16] the famous French obstetrician whose concern with the health of the infants he delivered was exemplary. He stated that infants should be given 10 per cent of their body weight as boiled cow's milk, and this 10 per cent rule was used also by Pfaundler, Holt, Sr., and Marriott and Jeans who added carbohydrate and water to the milk to make up caloric and fluid requirements, more dilute feedings being used for infants in the first month of life. The procedure suggested by Powers, that milk mixtures provide two-thirds of the caloric requirements as milk and one-third as added

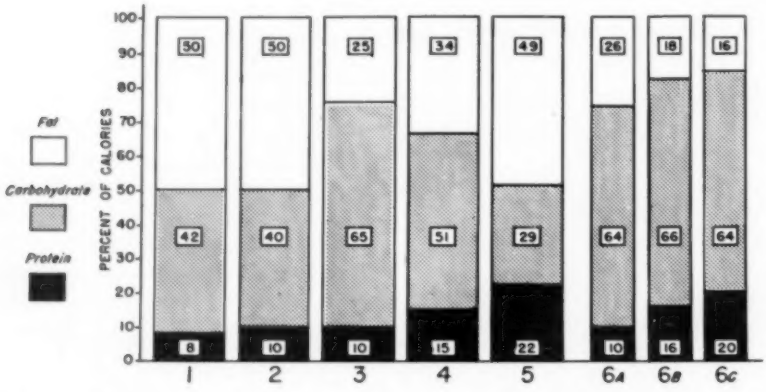

Fig. 1—The percentage of total calories in protein, carbohydrate, and fat. (Taken from Powers[12, 14] with slight modifications.)

1, Mature human milk (with 7 to 8 per cent of its calories derived from protein) and some cow's milk mixtures early designed to simulate human milk.

2, Proprietary mixtures designed in this country to simulate human milk in protein content have 9 to 10 per cent of the calories as protein which is approximately 20 to 25 per cent more than in human milk.

3, Sweetened condensed milk.

4, *The majority of cow's milk mixtures currently used in the feeding of well babies are in this group in which protein supplies 13 to 16 per cent of the calories.*

5, Whole cow's milk without added carbohydrate.

6a, A concentrated partially skimmed cow's milk to which carbohydrate was added, used in France in feeding well babies. It is remarkably similar to sweetened condensed milk in its distribution of calories.

6b, A simple mixture in which milk from which half the cream has been removed supplies $\frac{2}{3}$ of the calories and added carbohydrate the remainder; used extensively for feeding of premature and sick infants.

6c, Buttermilk-sugar-flour mixtures used traditionally in Holland; also a simple half-skimmed milk mixture with added carbohydrate used for feeding premature infants.

carbohydrate, also gives this approximate distribution. The extensively used feeding mixture of 1 part evaporated milk, 2 parts water, and 5 per cent of the *total* volume as added carbohydrate conforms to this recommendation. Heubner and Hoffman in 1891 and Marfan[15] in 1930 recommended feeding mixtures with this distribution of calories, and Kleinschmidt's 1920 modification of the butter-flour mixtures also yielded this distribution of calories. The feeding mixture used by Powers for feeding of premature infants and sick infants supplies 16 per cent of the calories from protein, but only 18 per cent from fat (Fig. 1, column 6b).

Finally we come to the feeding mixtures which supply 20 to 22 per cent of the calories as protein. Whole cow's milk has the distribution of calories noted in column 5. Budin recommended the use of undiluted boiled cow's milk in the feeding of infants. Harris[17] has reported on the successful use of 3 parts whole cow's milk and 1 part water or 2 parts evaporated milk and 3 parts water without added carbohydrate. The Dutch buttermilk-sugar-flour mixtures (column 6c) supply 20 per cent of the calories from protein, as does a partially skimmed cow's milk mixture used extensively for feeding premature infants.[18]

TABLE I

RELATION OF PROTEIN INTAKE TO TOTAL CALORIES INGESTED				
	A	B	C	D
Total calories per kilogram	100	120	133	150
Per Cent of Calories		*Protein Intake* (Gm./kg.)		
8	2.0	2.4	2.7	3.0
10	2.5	3.0	3.3	3.8
15	3.8	4.5	5.0	5.6
20	5.0	6.0	6.7	7.5
RELATION OF PROTEIN INTAKE TO DILUTION OF FEEDING MIXTURE*				
	0.8 cal./c.c. 24.0 cal./oz.	0.67 cal./c.c. 20.0 cal./oz.		0.5 cal./c.c. 15.0 cal./oz.
Per Cent of Calories		*Protein Intake* (Gm./kg.)		
10	3.0	2.5		1.9
15	4.5	3.8		2.8
20	6.0	5.0		3.8

*All intakes are calculated at 150 c.c. per kilogram.

In Table I protein intakes in grams per kilogram per day are related to the total caloric intake or dilution of the feeding mixture with the volume of intake kept constant, according to the distribution of calories of the feeding mixtures described in Fig. 1.

As already mentioned, one can, with relatively little soul-searching, estimate the protein allowances of breast-fed infants, but how shall one convert the data in Fig. 1 and Table I into an acceptable protein allowance for infants who are not breast fed? The general use of feeding mixtures such as those in column 4 of Fig. 1 will result in protein intakes of approximately 3.8 to 5.6 Gm. per kilogram per day when the total caloric intake is between 100 and 150 cal. per kilogram per day (Table I).

To the extent that this practice has been determined by an empiric observation such as that of Budin and others, that infants thrive when they receive 10 per cent of their body weight as cow's milk, it represents valid evidence for estimating 3.5 Gm. per kilogram as a recommended allowance. If, however, 100 c.c. of cow's milk per kilogram is recommended because the allowance has been set at 3.5 Gm. per kilogram, one falls into circuitous sophistry compounded by making of the 3.5 Gm. not an "ample allowance" but a *requirement*.

One needs then to ask what evidence there is that infants thrive better or worse on more or less protein than 3.5 Gm. of protein per kilogram. It is of interest to try to analyze some of the clinical experiences which have led to the general use of the feeding mixtures described in column 4. Before the general recognition of the benefits of heating cow's milk to sterilize it[19] and render it more digestible,[20] Biedert,[21] on the basis of chemical analyses of milk and inspection of stools, attributed the poor progress of artificially fed infants to the higher protein content of cow's milk. This led to various dilutions and modification of cow's milk to give feeding mixtures which more or less resemble breast milk in composition of known nutrients. The Moro butter-flour mixtures which correspond to column 2, Fig. 1 were, however, derived by physicians from traditional feeding practices of Alpine peasants.[22] The reasons that many of these feedings may not have survived in general use are multiple: (1) early, the milks were not heated and may have been grossly contaminated, (2) the dilution lowered the intake of other important nutrients such as calcium and vitamins, (3) the preparation of some of the feeding mixtures was too complex.

In the milk mixtures in which the goal of "simulating" human milk was attained by great dilution of *unboiled* cow's milk and addition of carbohydrate, there was the same failure to thrive that is even now seen in young infants who have the misfortune of being deprived of the breast in families where poverty dictates use of small amounts of milk in high dilution. How much of this failure to thrive is due to the low protein intake, how much to the decreased intake of other important nutrients in milk, how much to the increased incidence of infections stemming from use of contaminated milks or other concomitants of poverty such as overcrowding cannot be judged.[23] In 1950 Jeans wrote that when infants were fed lower amounts of cow's milk, which resulted in calcium and nitrogen retentions similar to those of infants fed human milk, they showed slower linear growth and poorer tissue turgor and motor development.[24] Since no data were published in support of this statement, it is not clear whether this was a personal observation. If it were, one can assume that the infants received boiled cow's milk and supplements of cod liver oil and orange juice and that the failure of the infants to thrive was due to the low milk intake and not to contamination of milk or inadequate intake of at least those vitamins given as supplements.

The lack of conclusiveness of most of the data comparing the progress of

full-term infants fed "low" protein, e.g., 10 per cent of the calories, with that of infants fed "high" protein, i.e., 15 to 20 per cent of the calories, imparts value to the judgment of experienced clinicians who had had experience with both types of feeding. In 1930 Marfan[25] reported on 16 years of favorable experience with a milk mixture from which approximately half the cream had been removed and 12 to 15 per cent cane sugar added before concentration and subsequent dilution with water. Protein supplied 10.5 per cent of the calories, a level similar to that of condensed milk feedings which had been condemned in this country as inadequate in protein. The spur to widespread use of this preparation in France came from shortages of fresh milk caused by World War I, and Marfan attributed its benefits in infant feeding to its low bacterial count, its decreased fat intake, and the increased digestibility of the heated protein. In 1934, however, he reported that because of difficulties in obtaining the product just described, he was now using feeding mixtures of evaporated milk with added carbohydrate and water with good results.[26] Although the exact proportions of this feeding mixture were not stated, he had previously given as his basic feeding mixture dilutions of whole cow's milk reinforced with cane sugar in which protein supplied 14 per cent of the calories[15]; at intakes of 100 to 120 cal. per kilogram, this would have meant an ingestion of 3.7 to 4.5 Gm. per kilogram. Thus, this experienced clinician was now routinely feeding infants mixtures containing a higher proportion of calories from protein, but the decision to do so was apparently based on expediency rather than on firm beliefs concerning protein allowances.

Since Dr. Jeans was a careful clinician and investigator and a precise speaker, and since he and his American contemporaries, the great majority of whom recommended the higher protein intakes, had much greater experience with feeding problems than is currently available in the United States, one hesitates to disagree with their opinion without having unequivocal data to support this disagreement. Although such judgment may be disdainfully branded as "conventional wisdom,"[27] empiricism cannot be totally disregarded. Howland's words[21] of 1912 to 1913 still ring true, "It would not be too much to say that the majority of artificial feeding has been done and still is done empirically, by rule of thumb, and with excellent results. Empiricism here has frequently shown the way before there has been satisfactory explanation of the modus operandi of some procedure, while oftentimes, the explanation generally accepted has required revision though the fact established by observation has remained. Nevertheless, empiricism has also been responsible for the prevalence of many false ideas that have been rooted out only with great difficulty. Probably the reason for this is that the healthy infant has a great margin of safety."

From a careful survey of the literature, we have been unable to find studies on low intakes of cow's milk which either support or refute Jeans' statement. In Table II are presented

the estimated protein intakes of infants fed simple dilutions of 1 part evaporated milk with 2 parts of water (column A), 3 parts of water (column B), or 4 parts of water (column C), with carbohydrate added to yield 0.67 cal. per cubic centimeter. The writers' well-baby clinic experience, with the reported hunger of 6-week-old infants fed the first of these 3 feedings, makes us doubtful that infants can be satisfied with the other feedings described. Although we have had no experience with the feedings containing less milk or total calories per cubic centimeter, we are willing to accept the statement that infants so fed ingest larger total volumes which may result in vomiting and regurgitation.[15, 22, 28]

Table II. Simple Dilutions of Evaporated Milk With Added Carbohydrate Designed to Give Different Intakes of Protein*

	A	B	C
Protein intake (gm./kg.)	3.5	2.6	2.1
Evaporated milk (c.c.)	50.0	37.0	30.0
Carbohydrate (Gm.)	7.5	13.0	20.0
Water (c.c.)	100.0	112.0	120.0
Total	150.0	150.0	150.0

*All mixtures contain 0.67 cal. per cubic centimeter; daily protein intake is calculated from assumed intake of 150 c.c. per kilogram.

Meyer[29] has reported that 33 per cent of artificially fed newborn infants discharged from a group of hospitals in the United States were being fed proprietary milk preparations, a tribute to the advertising skill of their manufacturers. Since some were feeding mixtures in which protein supplied 9 or 10 per cent of the calories rather than 15 per cent, one can assume that these infants ingested (and presumably gained well on) less protein than if they had been discharged on customary simple evaporated milk mixtures with added carbohydrate. On how much less protein they thrived one cannot judge because there is no way to estimate the amounts ingested, how long they continued on the feeding mixture prescribed, or the time of addition of protein-containing semisolids.

Beal[30] has made careful estimates of the intake of food by thriving infants of "upper middle class" Denver families enrolled in the longitudinal studies of the Child Research Council. The infants for whom protein and other foodstuffs were estimated had been fed cow's milk mixtures with supplementary solids after the second or third month. The median protein intake was approximately 5.0 Gm. per kilogram during the first 6 months and 4.4 Gm. per kilogram during the second half of the year. The twenty-fifth percentiles were 4.4 and 3.8 Gm. and the seventy-fifth percentiles 5.6 and 4.9 Gm. for the two age groups, respectively. In a later compilation[31] five infants who had been fed cow's milk preparations simulating human milk plus semisolids, received average protein intakes of 2.7, 2.7, 2.8, 3.2 and 3.3 Gm. per kilogram during the first 1 to 6 months. One infant ingesting no solids had an estimated protein intake of 4.9 Gm. per kilogram during the first month of life—his intake averaged approximately 290 c.c. and 183 cal. per kilogram per day. As

yet, no data have been reported that have attempted to relate the progress of the infants in this study to their food intake. The care with which these infants have been studied and the multiple disciplines represented in the study group assure a multifactorial analysis of accurate data.

Since ad lib. feeding is an essential part of prolonged studies of this type, the experimental design hinders a conclusive answer to the question of whether increased intake of protein and other foodstuffs *result* in more satisfactory growth. Stuart and his co-workers[32] have reported the findings in two children chosen for presentation because of contrast. In one child high protein and caloric intakes were associated with growth in height and increase in muscle breadth, as judged by roentgenograms of the leg, which fell in the fiftieth to ninetieth percentiles of the Harvard study group. In the second child lower caloric and protein intakes were associated with changes which fell in the lower percentiles. A difference in inherent growth drive may have been responsible for the differences in both food intake and growth, and one can only speculate whether a compulsory increase or decrease in protein intake would have increased or decreased the rate of growth of these two children.

The same consideration applies for the infants studied by Nelson,[33] Jeans and Stearns,[34] and Fomon and May.[35] Infants studied by the earlier investigators received protein intakes between 3.2 and 4.3 Gm. per kilogram, while the ad lib. intake of the infants studied later averaged 3.3 Gm. per kilogram during the first 1½ months of life and 2.5 Gm. per kilogram between 4½ and 6 months of age. Infants in each group had growth curves (weight or height) near either the middle or lower percentiles for Iowa infants. Whether the latter would have grown more rapidly if given more protein and the former less rapidly if given less protein cannot be answered since the studies were not designed to give such an answer.

In Table III are presented data from a previously published study[36] which illustrate some of the difficulties in interpreting empiric and other studies in which ad lib. feeding is part of the design. Data are presented for 20 premature infants, all of whom received a feeding mixture in which protein supplied 20 per cent of the calories. All received the same poly-vitamin supplements but no other foods. All were chosen for the study of self-regulation because they were vigorous, sucked well, and were able to cry and maintain good color and stable body temperature without oxygen therapy or external sources of heat. The mean daily weight gains for the 20 infants for periods of from 8 to 25 days ranged, with one exception, from 12 to 18 and averaged 14 grams per kilogram of body weight. The mean daily caloric intakes ranged from 85 to 150 and averaged 119 cal. per kilogram. The results were interpreted to indicate that when excellent nursing service permitted, premature infants could thrive on a wide range of caloric intakes. The data are reviewed here, however, because it is obvious that with a fixed feeding mixture not only did the total caloric intake vary but also

the protein and mineral intake. The protein intake can be calculated as having varied from 4.3 to 7.5 Gm. per kilogram and the minerals in the same proportion. The data, as measured by the weight gain and general condition of the infants, indicate their ability to adapt to a varied caloric, protein, and mineral intake; they give no answer as to whether a lower or higher food intake even within the limits and under the conditions studied was preferable.

plied 2.2 Gm. per kilogram (7 per cent total calories) or as an evaporated milk formula in which protein supplied 4.8 Gm. per kilogram (16 per cent of the calories), the differences being adjusted by slight changes in per cent of calories derived from fat. The ash content of the evaporated milk mixture and human milk was not determined, but from analyses in the literature, it can be calculated that the infants fed the evaporated milk received approximately 2.8 times

TABLE III. MEAN DAILY PROTEIN AND CALORIC INTAKES OF 20 PREMATURE INFANTS ON SELF-REGULATORY FEEDING*

SUBJECT	OBSERVATION		MEAN WEIGHT (KG.)	MEAN DAILY WEIGHT GAIN (GM./KG.)	DAILY INTAKE	
	AGE AT START (DAYS)	DURATION (DAYS)			CALORIES (PER KG.)	PROTEIN (GM./KG.)
S5	8	10	1.7	14.0	85	4.3
I13	9	9	2.2	14.2	94	4.7
K11	7	16	2.2	13.4	94	4.7
G14	6	21	1.9	14.7	100	5.0
W12	4	25	2.0	13.7	101	5.1
O8	16	9	1.7	15.0	104	5.2
C9	14	11	2.1	13.0	106	5.3
F3	12	16	2.1	16.1	107	5.4
C2	12	15	2.4	12.3	115	5.8
C10	13	9	2.4	18.2	115	5.8
M19	45	15	2.3	12.4	121	6.1
C16	2	13	2.0	9.0	125	6.3
H18	20	14	2.2	16.0	128	6.4
H6	28	15	2.5	14.0	132	6.6
C1	19	8	2.1	15.0	135	6.8
J17	32	12	2.1	12.0	139	7.0
T15	20	14	2.1	14.7	140	7.0
W7	15	14	2.4	18.3	144	7.2
S20	31	16	2.1	14.5	149	7.5
G4	21	11	2.0	13.5	150	7.5
Mean	17	14	2.1	14.2	119	6.0

*Feeding mixture consisted of 18 Gm. of powdered ½-skimmed milk, 12 Gm. of added carbohydrate, and diluted with water to 150 c.c. (1 c.c. = 0.8 cal.).

Controlled Studies of Premature Infants.—The rate of weight gain of premature infants has been determined in two studies in which the caloric intake per kilogram of body weight was kept the same but the percentage of calories derived from protein was different. In the first study[18] infants were fed 120 cal. per kilogram per day either as processed human milk in which protein supplied 2.2 Gm. per kilogram (7 per cent total calories) or as an evaporated milk formula in which protein supplied 4.8 Gm. per kilogram (16 per cent of the calories), the differences being adjusted by slight changes in per cent of calories derived from fat. The ash content of the evaporated milk mixture and human milk was not determined, but from analyses in the literature, it can be calculated that the infants fed the evaporated milk received approximately 2.8 times as much ash as well as 2.2 times as much protein as the infants fed human milk. Over a 21-day period, the infants fed human milk gained 12.5 grams per kilogram of body weight per day and those fed the higher protein intake 14.1 grams per kilogram of body weight per day, a difference significant at between the 1 and 5 per cent level. For infants below the mean weight of approximately

1,600 grams, the weight gains were 11.7 and 14.9 grams per kilogram of body weight per day, and this greater rate of gain on the higher protein diets was also significant at between the 1 and 5 per cent level. Discussion of the further increase in weight gain which took place when a feeding mixture with low fat as well as high protein content was used is not pertinent here because of the differences in fat intake. Since caloric intake was adjusted to actual weight and the infants on the evaporated milk mixtures were gaining more rapidly, one can calculate that they received approximately 2 per cent more total calories over the 21-day period but gained 13 per cent more weight. This is in accord with observations of rats fed high and low protein diets,[37, 38] to be discussed later, and also with a study of full-term infants.[17]

Harris compared the rate of weight gain of a group of 116 infants who received a mixture of 2 parts evaporated milk and 3 parts water with no added carbohydrate with that of infants who received a mixture of 1 part evaporated milk, 2 parts water, and 5 to 8 per cent added carbohydrate. Since the volume of intake estimated for the second month was the same, one can calculate that the infants fed the mixture without added carbohydrate ingested approximately 20 per cent less calories and 20 per cent more protein to give the same total weight gain.

In the second study of premature infants, two groups of infants were fed either processed human milk or a cow's milk preparation designed to simulate human milk.[39] The feedings gave virtually the same percentage of calories as protein, 10.6 and 11.1 per cent, respectively, but the ash content of the cow's milk preparation was approximately 2 times higher than the human milk which it "simulates." (Although the information is public,[40] this difference between ash content of human milk and the cow's milk preparations designed to resemble it is sometimes not recognized by physicians subjected to advertising pressures.)

A third group of infants was fed a partially skimmed cow's milk preparation reinforced with carbohydrate and diluted with water, but this feeding differed not only in protein and ash content (the use of a carbohydrate preparation containing sodium chloride made its total ash content 4.1 times higher than that of the human milk) but also in fat and carbohydrate content. On the average, all of the infants received 82 cal. per kilogram per day for the 3-week period of study, this low intake being dictated by previous nursing and medical customs of the hospital nursery. The infants fed the low protein cow's milk preparation gained 10.6 grams and those fed human milk 7.9 grams per kilogram of body weight per day, the differences being significant at the 5 per cent or less level. Since the only difference between these two feedings was in the ash content, it is reasonable to accept a causal relation between the changes in ash content and the change in weight gain. However, it does not seem justified to attribute the increased weight gain noted with the ½ skimmed milk mixture, either in this or in the first study,[18] to increased ash content when the feeding mixtures compared

differed in protein and fat as well as in ash content.

Although the investigators were aware of factors requiring concern about partial coefficients of correlation, their discussion of renal handicaps in electrolyte and water excretion led them to suggest that the increased weight gains noted in the first study were due to inordinate water retention. There is no support for this view either in the studies of rats by Wallace and his associates[37] or in Fig. 2 which presents data from published studies of water balance in premature infants.[41] Apparently, the homeostatic powers of the premature infants studied were adequate to avoid edema which may occur over short periods and with a sudden change in diet.[42]

The differences in weight gain noted by Kagan for the infants fed low and high protein were not as large as in the first study, but it may be that the low caloric intake required greater use of protein as a source of energy and diminished the opportunity of showing differences due to its peculiar value for synthesis.

In both of these studies only a weight gain over a 21-day period under circumstances in which the general clinical condition of the infants

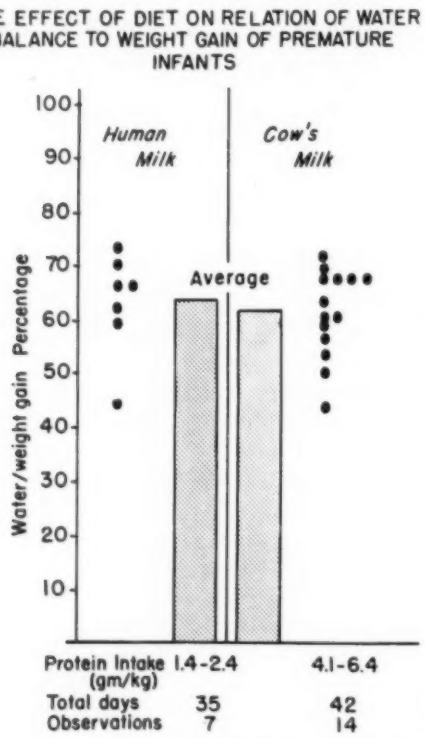

Fig. 2.—The relation of water retained to weight gain was determined in previous studies of water metabolism.[41]

was deemed satisfactory was considered as the criterion for judging the feeding mixtures, and this limited view of healthy progress is certainly open to criticism. Greulich[43] has reported a comparison of the physical growth and development of American-born and native-born Japanese children. He found the California Japanese children to be taller, heavier, and more advanced skeletally than the native Japanese children, presumably because of a more limited diet and other less favorable environmental conditions in Japan. The increased height and bone age reported by Bruch[44] for children with polyphagia make it reasonable to accept that Greulich's findings are at least partly attributable to dietary differences.

When one questions, however, whether this increased rate of growth is in itself good, there is no answer. Bigger is not necessarily better, but neither is it necessarily worse. In our current concern with the possibly harmful effects of overeating on degenerative vascular disease, it is important that we not discard criteria concerning gains in weight and height which have stood us in good stead for many years in estimating the progress of young infants. The data concerning the relation of nutrition to longevity[45] are sufficiently unsettled to lead us to hesitate before implying a significant relationship between intake of nutrients in early infancy, such as protein and the unsaturated fats of cow's milk, and degenerative vascular disease in adults, even though lipid deposition has been noted in infantile aortas. Whether habits of overeating in early infancy may condition eating patterns of significance for vascular disease in later life is another matter.

THEORETICAL FORMULATION OF THE PROTEIN REQUIREMENTS OF INFANTS

Hegsted[46] has made theoretical estimates of the protein requirements of infants. These are essentially estimates of a minimum requirement derived from calculations of: (a) basal metabolism, (b) an amount for growth on the assumption that total tissue gained is 18 per cent protein, and (c) an allowance of 10 per cent of the sum of these two to allow for losses in feces. The allowance for "maintenance" protein, 12.5 mg. of protein per basal calorie, is estimated from the urinary nitrogen excretion of animals of different species on intakes of no or minimal amounts of nitrogen.[47] No allowance is made by the author for increases in urinary nitrogen, stemming from the protein ingested to cover the basal calories or the growth allowance which during the first half year is larger than, or as large as, that calculated for the basal calories, nor for dermal excretion. The author is probably aware of some of these considerations, but he sweeps them aside with the statement: "We are not as much concerned here with the absolute amount, except that it is of the order of magnitude of 12.5 mg. protein per basal calorie." This generalization is difficult to understand. Does it mean that one may reasonably estimate minimal protein requirements in relation to basal calories up to 50 per cent but not 100 per cent more than 12.5 mg. per calorie? And if one is not concerned with the

absolute amount, how can one use it for the extensive calculations which the author has made for infants and children up to 18 years of age, allowing for variations due to differences in growth but not for variations due to differences between individuals? The protein requirement as estimated ranged from 2.3 to 2.4 Gm. per kilogram during the first month down to 1.4 to 1.5 Gm. per kilogram by the age of 4½ months. This happens to be not very different from the actual intakes of breast milk determined in ad lib. feedings of infants by Fomon and his co-workers,[48, 49] but as a minimum requirement, it throws doubt on the use of breast milk as a guide to "safe" allowances. In view of the theoretical objections noted, we do not believe that these theoretical formulations contribute to determination of protein allowances either in this country or elsewhere. This still requires actual testing of the effect on growth and health of different levels of intake of protein supplied in different diets.

EXPERIMENTAL STUDIES IN INFANTS AND ANIMALS

Nitrogen Balance Studies.—This brings us to a consideration of some of the data on nitrogen retention of infants fed different levels of protein in the diet which have been used in discussion of protein allowances. These may at first consideration, particularly by their collectors, appear precise, but for reasons which have been and will be discussed they have actually been condemned as sources of precise misinformation.[50] Furthermore, when one compares human milk with cow's milk, one compares complex foods with differences other than protein content, and only some of these may be known.[51] Finally, the use of the term biologic value[52, 53] only in terms of nitrogen retention carries the same danger as use of the high-power objective lens of a microscope in scanning tissues.

Comparison of human and cow's milk: Two studies have compared the nitrogen retention of infants fed human and cow's milk mixtures modified to give similarly low levels of protein intake. In one study of premature infants, nitrogen retentions were measured in two groups of 4 babies, each group fed on the average approximately 120 cal. and 2.8 Gm. of protein per kilogram per day.[54] Similar nitrogen retentions were found, but the investigators pointed out that this level of intake was well above what was generally regarded as a minimum and that the periods of study (total was 25 days in each group) were too short to assess biologic value. If proper statistical analyses had been made of these data, it would have been obvious that the data were inadequate to permit the impression given that human and cow's milk had protein of the same biologic value, even when the latter was considered in so narrow a frame of reference as ratio of nitrogen retained to nitrogen absorbed.

In a second study retentions were measured in 9 full-term infants fed lower protein intakes than in the first study (nitrogen × 6.25 = 1 to 3 Gm. of protein per kilogram).[55] Although

it was reported that the nitrogen retentions and weight gains were virtually the same, scrutiny of the experimental procedure and statistical analysis of the results make these conclusions unwarranted. Furthermore, the weight gains on these low intakes were frequently unsatisfactory, particularly in the observations on cow's milk. In 8 of 17 observations on cow's milk and in 3 of 10 observations on human milk, the gains were less than 20 grams daily, which is in itself a barely acceptable rate of gain for infants during the second month of life. Neither study fulfills statistical criteria which would permit one to state that the nitrogen retentions were the same or different,[56] let alone attempt to equate biologic value. Yet, such conclusions have been drawn from these data.[57]

In the studies of Fomon and his colleagues,[48, 49] nitrogen retentions were measured for infants fed either human or cow's milk over intermittent periods up to six months. The ad lib. method of feeding, the "homelike" atmosphere of the metabolic unit, the meticulous methods used in measurement, and analysis of intake and output in this metabolic unit with its long record of high repute yielded valuable data, but unfortunately the amount of cow's milk fed as a "simulated human milk" gave higher protein intakes than those fed human milk. Thus, no comparison of "biologic value" can be made from these studies, although the data are valuable in other respects.

The analysis of these three studies does not mean that the ingestion of equal amounts of human and cow's milk protein will lead to equal or different retentions; it says only that the data are not adequate to permit a conclusion either way.

Studies of amino acid metabolism: Since the adequacy of dietary proteins is presumably based on their content of essential amino acids, one might expect studies of amino acid requirements such as those of Holt and Snyderman and their co-workers to yield meaningful data on protein allowances. These studies were similar to those previously made by Rose and his associates in adults. The latter investigators fed groups of 3 to 6 normal male adults synthetic diets in which the nitrogen was supplied by mixtures of pure amino acids with added urea, glycine, or both and the energy and minerals were supplied from specially prepared wafers. Fat and water-soluble vitamins were given as supplements and, when necessary, added calories from butter fat and sucrose.[58] The investigators noted that when either mixtures of purified amino acids or hydrolyzed casein were used, the caloric intake necessary to convert a negative into a positive nitrogen balance was higher than when casein was fed as the source of the amino acids.[59] This suggests that the whole is greater than the sum of its known parts and is an important consideration in the interpretation of all data which are used for interpretation of protein allowances in terms of amino acid composition.

In the studies from which quantitative estimates were made, the objective was to discover for each of the essential amino acids the minimal intake which was capable of permitting positive nitrogen balance when

the diet furnished sufficient quantities of the other essential amino acids and an adequate supply of nitrogen for synthesis of the nonessential amino acids.[59, 61] In arriving at a minimal figure, we followed the procedure of inducing a negative nitrogen balance by decreasing the intake of the amino acid under study by 100 mg. a day and then raising the level by 100 mg. increments until a positive balance was attained. The figure for a minimum requirement in each subject thus represents the daily intake in grams per day below which a 100 mg. decrement produced a negative balance. Because of the small number of subjects studied, it was suggested that the maximum rather than the mean figure be designated *tentatively* as the requirement, that one designate twice the maximum as a *safe* daily intake, and that an optimal intake might be still higher. We have made a statistical analysis of these data and find that the maximum figure found for methionine could be calculated to cover 90 per cent of the populace, for leucine, lysine, phenylalanine tryptophane, and valine between 80 and 90 per cent, and for isoleucine and threonine less than 80 per cent of the populace. One can further calculate that to cover 99 per cent of the population the amounts needed vary from 116 per cent of the maximum observed for isoleucine to 272 per cent for threonine. These calculations have been presented in some detail because Rose's doubling of the maximum figure observed as a guide to a *safe* intake has been criticized; some justification of his procedure is supplied by this analysis, and the policy is certainly more in accord with customary thinking about ample allowances of food.

In the studies of infants by Holt and his co-workers,[62, 63, 64] who at first used hydrolyzed proteins and later mixtures of pure l-amino acids, the nitrogen retention and weight gain of infants were determined before and after reduction in the intakes of single amino acids. An exciting but unfortunate finding for the purpose of the investigators was that even complete removal of an essential amino acid sometimes permitted positive nitrogen balance. The investigators were thus compelled to use changes in slope of weight gain or differences in degree of positive nitrogen balance to judge "minimum" requirements. Furthermore, the difficulties of confining infants for prolonged metabolic studies and the lack of a sharp endpoint such as that available to Rose led to something less than a systematic graded withdrawal of the amino acid studied. The results are data which do not lend themselves to statistical analysis such as that used for the data of Rose and his colleagues. Although an answer to the question of minimum requirements is not forthcoming from the extensive studies, the apparently positive nitrogen balances with decreases in slope of weight gain even when an essential amino acid has been completely removed from the diet, and the increased caloric intake noted by these investigators as well as by Rose are challenging findings. The first suggests some peculiarity of metabolism of infants, the latter that these diets are lacking in some perhaps unknown factor or factors. Holt[65] has reported that even with the increased caloric intake the diets

become inadequate after 6 months. The implication is again strong that a good food like milk is greater than the sum of its parts, whether one considers this in terms of missing factors or imbalance between those present.[52, 66-68] Under these circumstances, one can use the known amino acid content of human or cow's milk as a criterion in designing studies of infants, but one has to expect disappointment in trying to judge allowances of whole proteins from studies other than those in which proteins are fed.

Comparison of nitrogen retention of infants fed different levels of protein: In general, studies of nitrogen retention of young infants fed different levels of protein have indicated that the higher intakes result in higher retentions whether these are referred to body weight or body weight gain. In studies of premature infants the daily retentions from diets which supplied 6 to 10 per cent of the calories as protein were 229 ± 6 mg. per kilogram of body weight as compared with retentions of 315 ± 9 mg. per kilogram from diets in which protein supplied 13 to 20 per cent of the calories.[69] The difference of 86 mg. per kilogram was almost 8 times the probable error of the difference. The higher retentions noted with higher intakes and the fact that the retentions were higher than those found by others in full-term infants at equivalent intakes were interpreted as due to the greater rate of growth of premature infants and the lower concentration of nitrogen in their bodies at birth.

In full-term infants studied intermittently over periods extending up to 6 months and more by Nelson,[33] Jeans and Stearns,[34] and more recently by Fomon and May,[35] the retentions of nitrogen were higher in a group of infants fed diets containing protein which ranged from 3.3 to 4.2 Gm. per kilogram than in infants fed between 3.3 and 1.8 Gm. of protein per kilogram. In Harrison's study,[70] however, 4 out of 5 infants of 4 to 7 months of age had virtually the same nitrogen retention when fed equicalorie cow's milk mixtures in which protein supplied 10, 15, or 20 per cent of the calories.

Objections have been raised to acceptance of the conclusions that increased protein intakes by rapidly growing subjects usually produce increased nitrogen retentions. These objections have been both methodologic and ideologic. The former refer to the difficulties in proper performance of balance studies. Variations in quality of data are due to unmeasured regurgitation, unmeasured residua on the inside of nipples and bottles, and unmeasured urinary, fecal, or dermal excretion. Unfortunately, these are all cumulative, tend to summate in the direction of suggesting increased retentions, and are exaggerated whenever the experimental diets are higher rather than lower in content of the nutrient studied. These were minimized in rigorous metabolic units such as the air-conditioned unit developed in the Cornell Department of Pediatrics by Levine. However, there are other handicaps: the number of infants studied and the duration of studies are limited by the magnitude and expense of the efforts required and by the lifted eyebrows of psychologically oriented medical and

nursing colleagues. Even though the artificiality of life in a metabolic unit can be decreased by techniques such as those early used by Jeans and Stearns and more recently by Fomon and May and their co-workers in the Department of Pediatrics at the University of Iowa, life in a metabolic bed, as in any hospital bed, cannot be considered a natural habitat, even for an infant. Such considerations have led to a dictum sometimes overlooked by hard-working investigators, that metabolic studies, like so many other physiologic studies, describe what may happen, not what must happen; metabolic data must be collected and analyzed precisely in order to permit even a semiquantitative conclusion, as for example that higher protein intakes by young premature or full-term infants lead to higher retentions than do lower protein intakes.

Studies of Animals.—The ideological objection to this conclusion is essentially the implication that if infants fed high protein retain more nitrogen than infants fed low protein, their bodies will differ in compositions. Wallace and his associates[37] and May[71] have recently restated this argument cogently. May has questioned the validity of both the old and new data on nitrogen retention in relation to body weight gain of infants fed cow's milk. Wallace and his co-workers have determined the body composition of weanling rats studied after 20 to 25 days on experimental diets of the following types: high protein–high electrolyte (HPHE), high protein–low electrolyte (HPLE), low protein–high electrolyte (LPHE), and low protein–low electrolyte (LPLE). Protein supplied 19 and 9 per cent of the total calories in the high and low protein diets, respectively, carbohydrate 28 and 38 per cent, and fat 53 per cent. The salt mixtures imitated the ionic ratios found in fat-free cow's milk, and a vitamin mixture was added to the diets in amounts calculated to make them equal. All animals had been weaned to a commercial feed of proved adequacy for growth and health of the albino rat before transfer to the experimental diets which were given for 20 to 25 days, a length of time which allowed approximate doubling of weight for the most slowly growing groups. In two other groups of animals, HPHE and LPLE, only food consumption and weight gain was measured. The experimental procedure is attractive because the two levels of protein used are approximately the extremes of those commonly employed in artificial feeding of infants.

As in other studies of animals, the investigators found a relative constancy in nitrogen, water, and ash concentration of the final fat-free body weights in the two groups. There were certain differences between the animals fed high and low protein, which suggest an answer to the ideologic problem. These are *the differences in rates of accretion.* The average daily total weight gain of the animals fed high protein was approximately 80 to 90 per cent higher than that of animals fed low protein. Since the final body concentration of protein was the same in both groups, obviously the former stored more nitrogen than the latter, both as total nitrogen and as total nitrogen per kilogram of average body weight per day. Even though the protein concentration of *the weight gain* is

calculated to be the same in the two groups, it is possible that if they had been sacrificed for analysis after *shorter periods* on the diets, that is, before they had reached a constancy of composition of 20 Gm. of protein per kilogram of fat-free solids, differences in protein concentration of the *weight gain* would have been found.

Repeated analyses of carcasses of animals and the few analyses of the bodies of humans indicate that "chemical maturation" consists, in a narrow nonfunctional sense, of an increase in protein and decrease in water concentration of the fat-free body weight or "lean mass" of the body. In the case of the rat this means a change in concentration of protein from 9 per cent of fat-free solids at birth to 15 per cent at time of weaning (which is when studies of effect of differences in diet can easily, and therefore usually, begin) to 20 per cent as the equilibrium or "maturation" point.[72] In the human the small amount of data from chemical analysis of the body indicate changes in protein concentration of fat-free solids from 14 per cent at birth to 19 per cent in adult life.[73]

In relating nitrogen balance studies to composition of body gain of infants, one has dealt until now only with total weight gain in which changes in the proportion of the total body weight contributed by changes in water, fat, and muscle mass have not been estimated. If methods of estimating lean body mass by studies of helium displacement can be adapted to infants,[74] the results of these plus estimation of changes in water content of the body plus estimation of changes in muscle mass, e.g., from creatinine coefficients, might give a basis for reference that would make carefully collected nitrogen balance data more acceptable. On the other hand, one would still have to question the significance for infant feeding of such data, if and when obtained, for statistical reasons already mentioned, i.e., the limitations of extrapolation from the metabolic unit to the infant populace at large. The technical problems in balance studies, particularly the customary failure to measure dermal excretion, plus the statistical considerations, tend to make all results at best only semiquantitative. Finally, the results of such studies fail to describe what is perhaps more important, namely, whether the infant fed higher protein functions differently from the infant fed low protein.

SOME EXAMPLES OF DIFFERENCES IN FUNCTION AS A RESULT OF DIFFERENCES IN DIET

One example of a difference in function as a result of a difference in diet is seen in the data on utilization of foodstuffs. In the studies of Wallace and his colleagues,[37] the food intake of two groups of animals was accurately measured for a period of 23 days. The high protein animals ate 12 per cent less food by weight (14 per cent less calories) and weighed 12 per cent more than the low protein animals. Calculating the calories utilized for physiologic activity indicated that the low protein animals expended 175 cal. more per animal during the period of observation and showed increased spontaneous activity which had been previously noted by others as a manifestation of nutritional inadequacy. On the basis of food, urine, fecal, and carcass

analysis in rats fed diets with different levels of protein, paired either to equal weight gain or equal food intake, Hamilton[38] noted similar differences in the relation of the amount of food ingested to nitrogen retention and weight gain. A similar conclusion may be drawn from previously mentioned observations of premature[18] and full-term infants.[17]

Another area of interest is in the relation of diet to infection. It has long been considered that a good diet protects against infection and morbidity or mortality therefrom. Some of the clinical and laboratory findings which one must try to interpret are as follows:

(a) Famine and pestilence go together, but the unsanitary conditions which accompany both, rather than the famine alone, may be responsible for the pestilence.

(b) Children whose diets have been severely lacking in protein and who do not yet show the classical picture of kwashiorkor may develop the full-blown picture as the result of acute infectious diarrhea, malaria, or contagious diseases of childhood.[75]

(c) The development of active tuberculosis lesions in adolescent children has been related to previous depletion of "protein reserves," as measured by high nitrogen retentions when these children were placed on adequate diets.[76]

(d) Patients with hypoalbuminemia[77] produce fewer antibodies in response to antigenic stimuli than those with normal serum proteins.

(e) Animals fed low protein diets have shown diminution[78] or no change[79] in response to antigenic stimuli.

(f) In experimental animals high protein diets have increased or failed to increase the rate or time of survival after injection of bacteria. Dubos and Schaedler[80] have reported that in mice on a diet adequate to produce similar weight gains greater susceptibility occurred on an 8 per cent casein diet than on a 20 per cent casein diet. They also reported that supplementation of the former diet with an amino acid mixture to the level of the organic nitrogen content of the latter decreased the susceptibility of the mice. The investigators believe that their use of young growing mice may have sharpened and made the results of their experiments more consistent than some of the controversial results in the literature to which they refer. With some viruses, on the other hand, low protein diets have led to a greater survival, and with some there have been cyclic changes: during the early days of low protein feeding the survival rate is diminished, to be followed by increased survival as the low protein diet is continued, and finally by decreased survival as protein depletion continues.[81]

Demonstration of differences apparently depends both on the organism used (virulence, intensity of exposure, and species, i.e., whether bacteria, viruses, protozoa, helminths, or Rickettsiae) and the host, whose reactions may be conditioned by genetic constitution, dietary intake, as of protein or vitamins, steroid production or administration, and previous exposure to organisms or antigens.[82, 83] In view of the complexity of the factors affecting the course of

infections, Schneider[84] has warned experimental nutritionists to tread lightly. Clinicians must be even more cautious in the interpretation of the relation of diet to human infections; this, of course, does not mean that one push aside the need for maintenance of good nutrition in patients suffering from acute or chronic infections.

The differences in utilization of foodstuffs noted, differences in antibody production, and the course of infection as a result of differences in protein intake bespeak differences in intracellular transformation of nutrients and these might be expected to be mirrored in changes of enzyme activities. Such changes have been summarized by Knox and his associates.[85] Some enzymes which directly vary in activity with the protein content of the diet, either by an increase or a decrease or both, are liver xanthine oxidase, arginase, uricase, alanine-glutamic transaminase, adenosinetriphosphatase, and pancreatic trypsin. Others which show no change are liver catalase, muscle adenosinetriphosphatase, and kidney xanthine oxidase.

The reviewers are careful to point out that these changes may represent mechanisms of importance for the regulation of metabolism but do not carry a necessary implication of increase or decrease in fitness to survive. For example, the hypertrophy of the kidney in response to high protein feeding has been long known.[86] This findings has been used as a rationale for recommending a low protein diet for patients with chronic and acute nephritis, and the danger of work hypertrophy has been cited as a reason for recommending low protein feedings of young premature and full-term infants. However, it has been recently shown that high protein feeding increases renal concentrating ability both in adult humans and rats.[87, 88] How shall one judge whether increasing the load of solutes claiming excretion by the kidney of the young infant decreases or increases his powers of adaptation? How does one balance "rest" and "exercise" in making the liver, the heart, the kidney more fit for stress? Are there necessary detoxifications in the human that would be aided by high protein feeding just as detoxification of 2-amino-fluorine by the dog[89] is aided by high protein feeding? These considerations may be of no importance at the levels of protein intake about which there is controversy in this country, but they may be very important in areas of prolonged low protein consumption.

SOME ADDITIONAL COMMENTS AND PRACTICAL CONCLUSIONS

It is obvious that the data are not adequate to permit a decisive recommendation for either "safe minimum" protein allowances as in the report of the F.A.O. or for the ample allowances which are the goal of the Food and Nutrition Board. Differences in interpretation arise which may be likened to the differences in colorimeter readings one obtains with different filters. Pediatricians concerned with parathyroid-renal homeostasis and the occurrence of tetany in very young infants who have been fed excessive amounts of undiluted cow's milk without added carbohydrate wish the protein allowances set

low in the hope of assuring low intakes of cow's milk and, therefore, of phosphate. Concern with handicaps in renal homeostasis which may permit development of hyperelectrolytemia under stress of water deprivation or excessive water loss also leads to preference for lower protein intake, although the direct concern is really for more water. The biologist takes as his guide the protein intake of breast-fed infants, and in the absence of data indicating a marked inferiority of cow's milk to human milk protein, he considers it unphysiologic to recommend a cow's milk protein allowance which is 75 per cent higher than that ingested in human milk. This view neglects the possibility that decreases in cow's milk intake to equivalent protein intake may excessively lower the intake of other important nutrients in cow's milk. Unwillingness to try to modify cow's milk to resemble breast milk might even be considered evidence of greater faith in the biologic value of breast feeding. The internationalist confronted by locally decisive food habits and shortages of animal proteins and money welcomes a lower recommendation, particularly as a guide to further studies. Manufacturers of proprietary mixtures will be found on either or both sides of the problem, depending on their vested interests. (A Physicians' Council for Information on Child Health has been formed to protect physicians from at least the less subtle misinterpretations of inconclusive data.) The psychological approach to infant feeding, now so popular both as a reaction to past rigid feeding practices and as part of the general psychiatric orientation of the populace, trusts the mother's interpretation of the infant's hunger to decide his food intake. The infant's and the mother's personalities, as well as the source of the counselling on infant feeding, become the determinants. In this country this leads to a high protein intake. Finally, one comes to what might be called a pragmatist's approach. He says that since for several decades an overwhelming majority of the artificially fed healthy infants in this country have received feeding mixtures in which protein supplied approximately 15 per cent of the calories and since the average intakes of 100 cal. per kilogram represents approximately 3.5 Gm. of protein per kilogram, why not recommend this as the allowance? To the extent that such a recommendation interferes with the conduct of critical studies of minimal allowances in countries which cannot afford ample ones, this view is untenable; a clear understanding of both the purposes of the *Recommended Dietary Allowances* and the nature of the evidence on which they are based should prevent such a result.

As stated earlier, we would have preferred that the Food and Nutrition Board accept 3.5 Gm. per kilogram as the recommended daily protein allowance rather than the lower ones suggested by Gyorgy and other advisors. In essence our opinion was derived from the failure of the evidence now available to contradict the formulations of eminent American pediatricians whose extensive experience included opportunities to observe both high and low protein feedings. Personal experience with the hunger of infants fed even 3.5 Gm. per kilogram makes us unwilling to recommend intakes of cow's milk

which would give less protein. Although the determinants of food intake are complex,[90, 91] the possibility exists that unmet nutritional needs may make the intake of 3.5 Gm. and more of cow's milk protein per kilogram necessary, particularly when simple mixtures easily available to the whole populace are used. This implies that cow's milk may lack other nutritional factors, the needs for which are not met by feeding cow's milk in amounts less than 100 c.c. per kilogram. The protein allowance then becomes, as it should, a consideration secondary to the milk allowance.

What practical conclusions can one make for infant feeding? First, breast feeding of full-term infants should be encouraged not only for reasons of emotional gratification, cleanliness, and simplicity but also because of easily obtained nutritional benefits. Second, when breast feeding is not possible, the use of 1 part evaporated milk, 2 parts of water, and carbohydrate to make up caloric requirements in mixtures which give 100 c.c. of cow's milk per kilogram will give both ample protein and ample water in relation to solute load. The use of somewhat more dilute feedings such as 1 part evaporated milk, 3 parts water, and 5 per cent added carbohydrate (16 cal. per ounce) during the first few days or week of life will avoid undue strain on gastrointestinal, renal, and endocrine homeostatic mechanisms of the newborn infant. Such a dilute feeding mixture was widely used several decades ago on the general principle that one shouldn't rush new babies just as one shouldn't rush new automobiles; physiologic investigations merely supply the detailed reasons for a principle which was well established before the general speed up of our way of life. The increased use of proprietary preparations is the result of subtle and not so subtle advertising pressures on physicians who either have never learned, or forgotten, certain basic facts about infant feeding.

In the feeding of premature infants, both metabolic and carefully collected clinical data indicate that they should be given more protein than full-term infants. How much more is not clear, but infants have gained well on feeding mixtures in which protein supplied 16 or 20 per cent of the calories. At 100 to 120 cal. per kilogram, this is the equivalent of 4 to 6 Gm. per kilogram. No proof has been presented of the harmfulness of such intakes, but concern has been expressed about the increased solute load. Studies of water metabolism have shown, however, that the lowered insensible perspiration of premature infants makes more water available for urine.[13] Here again it is important to go very slowly during the first week or two of life. However, the problem is complicated by the fact that simple dilution of the feeding mixture as practiced for the full-term infant is more difficult because of the inability of the infant to suck and swallow. No generalizations are possible because practice will depend on the vigor of the infant and the quality and quantity of nursing service.

SUMMARY

A review has been made of some empiric and experimental data available for estimating the protein allowances of young infants. Infants apparently thrive for the first six

months of life on protein intakes which vary within the ranges contained either in breast milk or the artificial feeding mixtures customarily used in this country. The lack of conclusive data in support of one figure or another is partly a reflection of the adaptive power of infants. When breast feeding is not possible, the reviewers favor the higher protein feedings because of their simplicity.

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Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, ***Editor***
John M. Craig, ***Assistant Editor***

CASE 1.—This 14-year-8-month-old white boy, over the first 14 years of his life had ten hospitalizations for respiratory infections which began at 4 weeks of age. Over the 8 months prior to entry he had two further hospitalizations for respiratory distress and a chronic cough, which was productive of yellow sputum and worse at night. One month before admission to The Children's Medical Center, he was admitted to another hospital where a diagnosis of asthma was made. During this hospital admission he had what was believed to be an episode of status asthmaticus, and received epinephrine, cortisone, aminophylline and oxygen. He improved slightly after this and was discharged, still in poor condition, to be admitted 24 hours later.

The boy was one of six siblings of a family in poor economic circumstances. There was no family history of diabetes, asthma, tuberculosis, or cystic fibrosis of the pancreas. The boy has smoked since the age of 5 years, using five to six cigarettes a day, usually recovered from the street.

On admission the vital signs were: temperature 104° F., pulse 160, and respirations 52 per minute. The boy was acutely ill and dyspneic, with flaring alae nasae and severe suprasternal retractions. He used all the accessory muscles of respiration. A purulent postnasal discharge was present. The anterior-posterior diameter of the chest was increased, and marked hyperresonance over both chests was elicited. The air exchange was poor and the breath sounds were faint throughout, though accompanied by coarse rhonchi. The heart and the remainder of the physical examination were normal. No clubbing of the fingers was present.

The leukocytes numbered 27.3 thousand per cubic millimeter; the differential count was: polymorphonuclear cells 86, lymphocytes 3, monocytes 2, and atypical lymphocytes 9 per cent. Blood cultures and tuberculin reaction (1:500) were negative. The culture of the nose and throat grew a few colonies of *Staphylococcus aureus*. The test for determination of elevated sweat electrolytes was negative. Roentgenograms of the chest revealed a peribronchial infiltration in both lower lung fields; the remainder of the lung fields were hyperaerated but otherwise normal. The outline of the heart was normal.

The patient was treated with penicillin and oxytetracycline. He gradually improved, though after three weeks he still had episodes of severe coughing, retraction, and definite hoarseness. A bronchoscopy was performed three weeks after admission.

DR. JAMES B. DEALY, JR.*—It would appear from the protocol that this boy, with a significant recent weight loss, had a serious illness. The history of repeated hospitalizations for respiratory infections prompts a consideration of predisposing factors. The admission physical findings of an acutely ill, cachectic, air-hungry child using all his accessory muscles of respiration, plus a rapid pulse, poor air exchange, substernal retraction, and coarse rhonchi throughout his lungs fit the clinical syndrome of asthma.

The roentgenograms of the chest, as described in the protocol, show some thickening of the intrapulmonary markings in the right lower lung field. It is worth pointing out, however, that the medial portion of the right lower lung field is one of the most difficult areas to assess by virtue of the fact that the x-ray penetrates a greater depth of lung tissue here than elsewhere. In other words, this area is normally more heavily populated with lung densities. The second area of the chest in which there is an apparent increase in lung markings is along the left heart border just above the diaphragm. In the lateral view there is evidence of hyperaeration, which can best be seen in the anterior mediastinal region.

*Dr. Dealy is Radiologist-in-Chief at the Peter Bent Brigham Hospital and Assistant Clinical Professor of Radiology, Harvard Medical School.

The patient had cough with retraction and hoarseness, yet I can recognize no abnormality in the shadows of his larynx or trachea.

In summary, we have a child with recurrent respiratory infections dating back to early infancy. He does develop the clinical syndrome of asthma, but its onset so early in life does not suggest ordinary asthma and makes one search for some predisposing mechanism or defect. One might suggest an abnormality in gamma globulin formation, such as congenital hypogammaglobulinemia. If this be true, one would question the advisability of giving cortisone to a patient with immunological responses already impaired.

A *forme fruste* of cystic fibrosis of the pancreas with pulmonary involvement is, I suppose, a possibility; but there is no family history of mucoviscidosis and he had a negative sweat electrolyte test. I believe it is the experience of the group in New York that bronchiectasis, which always comes up for consideration in the differential diagnosis of increased lung markings on plain film x-ray studies, is a late complication—by which time, the diagnosis ought not to be in doubt. I really don't think one has much to go on to support either of these possibilities. In fact, I cannot make a specific diagnosis on the basis of the information given. I might say that I don't know why this patient had recurrent asthmatic episodes and recurrent basal bronchopneumonia.

DR. CRAIG.—I wonder if the physical signs described in this case are really those of asthma? The protocol described respiratory distress, but says nothing about a prolonged expiratory

phase in his respiratory cycle. The adventitial sounds, too, seem to me to be not those of asthma. The protocol describes coarse rhonchi, not the usual irregular high-pitched squeaks and groans. Is there anything on the chest films that really suggests that this is asthma?

DR. DEALY.—By x-ray there is nothing necessarily characteristic about the asthmatic chest except that the lungs tend to be voluminous and hyperaerated. With recurrent bronchitis or respiratory infections, there may be a diffuse nonspecific prominence of the more "central" lung markings. The film taken four to five months after this patient was treated looks essentially normal to me. Asthma is not diagnosed definitely by x-ray.

The symptom that worries me in this case is the persistent hoarseness. During the acute episode described in the protocol, it could have been related to high airway obstruction, yet I see no confirmatory evidence of this.

DR. FARBER.—Could you ascribe his hoarseness to his long history of cigarette smoking?

DR. DEALY.—He smoked only four to five cigarettes a day and these only partially. I doubt if this was a sufficient irritant to cause hoarseness.

DR. FARBER.—Did you consider the possibility of infection produced in that way?

DR. DEALY.—That is certainly possible, although I cannot suggest what specific infection it might be.

DR. FELIX HEALD.—Would you consider a congenital defect in the larynx or trachea as a possible cause for this boy's long-standing respiratory difficulty?

DR. DEALY.—I meant to imply with my comments about his hoarseness that this should be considered along with the other predisposing factors mentioned. Since the roentgenogram of the trachea appears normal and I don't have information on any abnormal behavior of the trachea during the various phases of respiration at fluoroscopy, I cannot make such a diagnosis.

DR. HARRY L. MUELLER.—I am inclined to agree with Dr. Craig, that there is very little evidence that the patient had asthma. If the diagnosis is based solely on the presence of wheezing and respiratory distress, possibly he did have "asthma." But if the diagnosis is established on the basis of an antigen-antibody reaction causing bronchospasm, I think there is very little evidence for this diagnosis. Even though he received vigorous therapy directed to an asthmatic condition, including aminophylline, epinephrine, and cortisone, there is not much evidence that he got any response from these. There is no history of atopy in this child, or his family, so I think it is quite unlikely that this child had asthma. I would agree with Dr. Dealy that there was metabolic or congenital abnormality that predisposed him to repeated pulmonary infections.

DR. FARBER.—Would any of the fourth-year students like to offer a diagnosis?

A FOURTH-YEAR STUDENT.—I have seen one young adult, 22 to 24 years of age, who had multiple papillomata of the larynx, trachea, and proximal bronchi and had a history very similar to this.

DR. EDWARD B. D. NEUHAUSER.—I think both this case and the next are most difficult to diagnose from the

data given. In this case it seems to me that the clinical picture of a severely ill child with hyperaeration, air hunger, and acidosis is quite out of keeping with the minimal roentgenographic signs at the right base. One would think of some severe upper airway obstruction, as in diphtheria, to explain the clinical picture.

mucosa being normal. The largest of these masses was about 0.5 cm. in diameter, and altogther they formed a heaped mass which measured 2 by 2 cm., the individual lobules being less than 1 mm.

Histologically, these lesions are characteristic of transitional cell papillomata of the larynx and trachea.

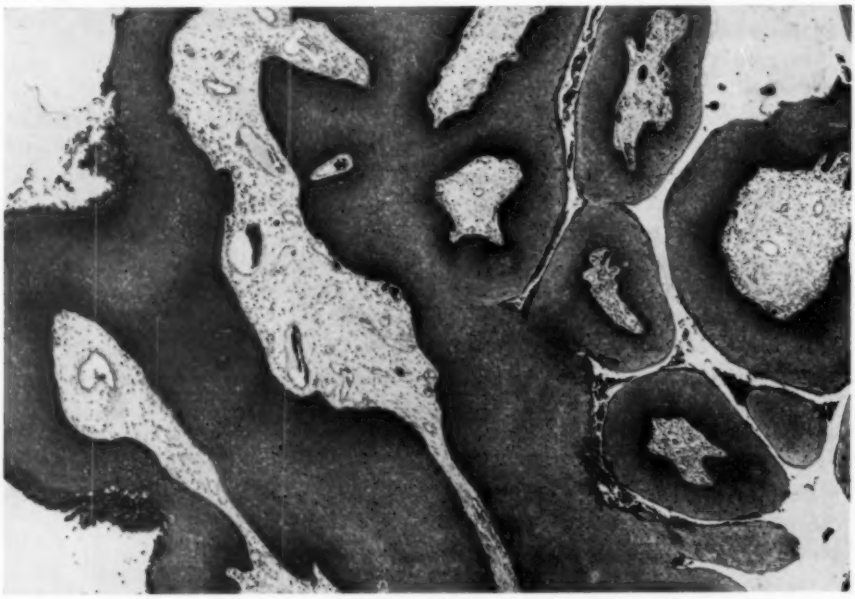

Fig. 1.—Case 1, Polyp. There is a broad band of epithelial cells surrounding a fibrous tissue core in a multivillous polyp. (Toluidine blue eosin ×140.)

Dr. Gordon F. Vawter.—The child was bronchoscoped and the findings led the surgeons to omit doing a bronchogram. The larynx, at that bronchoscopy, was found to be normal in all respects, but protruding into view below the larynx there were masses of yellow-gray tissue, rather firm, which could easily be avulsed with a small amount of bleeding from the tracheal wall. About fifteen such lesions were present and scattered along the trachea, the intervening

They have a relatively avascular edematous branching stromal core and a nonkeratinizing epithelium covering the surface (Fig. 1). No inclusion bodies are found in these cells, nor is there any inflammatory reaction in the tissue.

A subsequent laryngoscopy and bronchoscopy one month after operation showed complete healing except for an area of roughening above the carina.

This, then, represents a case of multiple papillomata of the trachea. All of the reported cases are multicentric, having seeded along the trachea. There are many more unreported cases of simple solitary lesions and, hence, less dramatic. Since the work of Ullman,[1] in 1923, these have been considered to be caused by an easily transmissible viral agent, because he could produce lesions in the tracheas of experimental animals by the use of Berkefeld filtrates of the tumor. This transmissibility may be of considerable importance in the dissemination of the lesions within the tracheal-bronchial tree.

The disseminated lesions produce characteristic circular densities with a central area of less dense parenchyma in the roentgenograms when they involve the lung proper. There may be latent periods of up to five to ten years from the onset of symptoms before such pictures develop.

DR. CHARLES F. FERGUSON.—I have not followed this child after the second bronchoscopy. We do know that papillomata usually recur. The histology of the papilloma we see in the larynx is the same as that in the trachea. We have searched over the years for some specific therapy because of their marked tendency to recur, and although they are benign, they cause so much destruction of the larynx that they become great problems.

At the recent International College of Otolaryngology meeting, during the entire morning session, many treatments were recommended but there is no satisfactory therapy. A series of cases has been reported in which tetracycline and oxytetracycline have been used over a long period of time with some success. Podophyllotoxin has also been used because of the similarity of such lesions to condyloma accuminata. Our impression was that this material enhanced the rapidity of growth of the lesions. We gave up its use after a patient coughed in my eye and I developed a severe conjunctivitis. It has extremely irritating properties.

There has been no progress in the last 23 years in their treatment. Removal is still the preferred treatment, although with repeated removal the rapidity of growth often appears enhanced.

DR. DEALY.—What is the youngest age at which the lesion has been described?

DR. FERGUSON.—We have seen them in infants 4 months of age. Some have even been considered congenital in nature.

DR. DEALY.—We had a very pleasant symposium at the Brigham not too long ago on the treatment of warts. A good deal of time was spent on a discussion of psychiatric therapy of warts. Perhaps this is one phase of therapy, Dr. Ferguson, which wasn't adequately explored!

CASE 2.—This 9-year-old white boy was admitted to The Children's Medical Center with an 8-week history of cough and intermittent fever to 104° F. A one-week course of oxytetracycline gave temporary improvement. Chest roentgenograms made three weeks and again five days prior to admission were interpreted as pneumonitis in the left lower lung field. The past and family histories were not contributory.

Vital signs on admission were: temperature 100° F., pulse 114, and respirations 25 per minute. The child was well developed and in no distress, though thin. The only positive physical findings were in the chest, where there was dullness to percussion and decreased breath sounds and tactile fremitus in the left posterior chest. The heart was normal to examination except for a soft Grade 1 systolic murmur at the apex.

The urine examination was within normal limits. The hemoglobin was 12 Gm. per cent and the leukocytes numbered 12.4 thousand per cubic millimeter. The differential count was: polymorphonuclear cells 80, lymphocytes 16, monocytes 1, and eosinophils 3 per cent. A tuberculin test in a 1:100 dilution was negative. The estimation of sweat electrolytes gave normal values. The nose and throat cultures grew a few colonies of *Staphylococcus aureus*. Roentgenograms of the nasal sinuses were clear. A film of the chest revealed an infiltration and diminution in volume of the left lower lobe. There was no hilar lymphadenopathy and the lung fields elsewhere were clear. Two days after admission a bronchoscopy and bronchogram were performed.

DR. DEALY.—On the plain films, a zone of increased density may be seen projected through the heart shadow. This is consistent with the findings of regional atelectasis on physical examination. In the posteroanterior film of the bronchogram, we see both saccular and cylindrical bronchiectasis involving all three major basal divisions of the left lower lobe. There is poor filling of the superior segment of the left lower lobe, unassociated with demonstrable intrinsic deformity. There is also poor filling of the lingula but, again, I can see no distinct abnormality.

A constant finding on all films is narrowing of the entire segment of the left lower lobe bronchus (Fig. 2). However, the caliber of the lumen is not greatly compromised, which would imply that the degree of obstruction had been greater in the past than it was at the time of the bronchogram (and of sufficient degree to have caused complete collapse). There then developed an irreversible bronchiectasis.

In addition to the narrowing of the left lower lobe bronchus, there is definite displacement of it and an indentation that has a rather sweeping radius of curvature. I cannot identify a contiguous parenchymal density in this region. There is, however, a very faint, circumscribed soft tissue density which is tempting to regard as a space-occupying lesion. I wish I had not seen this, since it is quite removed from the left lower lobe bronchus where the difficulty must reside, and I don't know how to interpret its significance. There is no hilar adenopathy.

In this second patient we are dealing with a problem of local segmental collapse and one must entertain the various possible etiologies. Before enumerating the more probable ones, it is worthwhile to point out that we would have to consider sequestration of the lung. I think that this can be ruled out quickly, since none of the cases described in the literature thus far, to my knowledge, have had a bronchial communication demonstrated by bronchography.

Has the child aspirated a foreign body? I suppose that this is entirely possible. All I can say is that there is no history of aspiration, nor do I see a foreign body on the bronchogram as a discrete localized intraluminal filling defect.

One would have to consider the possibility of tumor. This patient did not smoke (as opposed to the first patient), so perhaps we need not consider very long the remote possibility of bronchogenic carcinoma! In the adult-age group, of course, it is proper

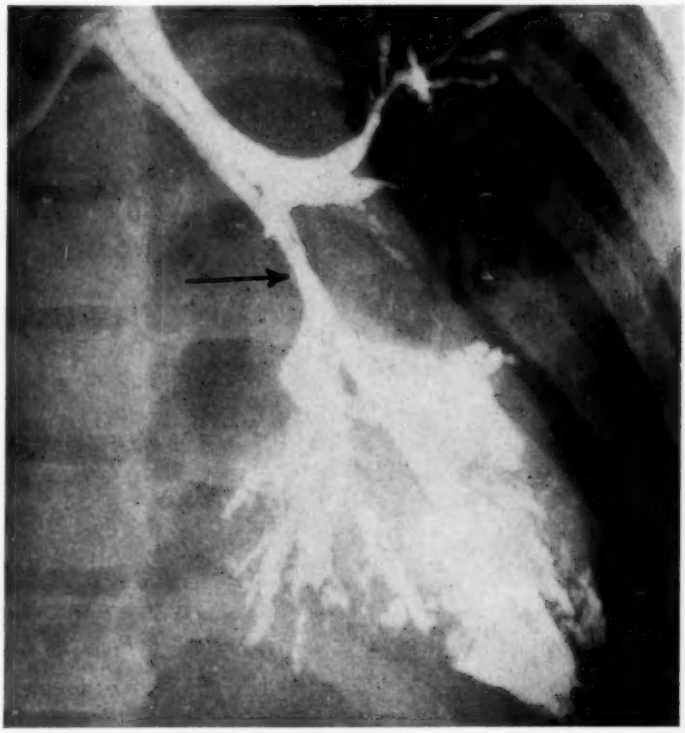

Fig. 2.—Case 2, Bronchogram. A narrowing and bowing of the lower lobe bronchus is present at the arrow.

Could it be an inflammatory process involving the left lower lobe bronchus with intermittent episodes of varying degrees of obstruction? I suppose this is also entirely possible. Tuberculous bronchiectasis is not very common and the child's tuberculin test was negative so that if it was an infectious process I should think that tuberculosis would be unlikely.

to regard any localized pulmonary collapse as being on the basis of bronchogenic carcinoma until it is proved to be something else. Another form of tumor would be a bronchial adenoma, even though this, too, as far as I know, would be quite rare in this age group. It is awfully tempting, on the basis of the bronchogram, to regard the displacement of the left lower lobe

bronchus as due to the intrapulmonary portion of a dumbbell-shaped bronchial adenoma.

I am not completely familiar with the varied gross morphologic patterns of bronchial adenomata in children, but in young adults, where the incidence is divided equally between males and females, they fall into three general types: those that are sessile, those that are of the dumbbell or iceberg type, which may have a relatively small intraluminal component in relation to a larger intrapulmonary component, and those that are pedunculated or on a stalk. Some of the last type have been removed bronchoscopically.

The final thing I would consider would be a local malformation of the bronchial wall with a resultant intermittent partial obstruction. Perhaps I should combine the appealing possibility of a bronchial adenoma with this by suggesting that the defect might have been in the nature of an adenomatous malformation of the bronchial glands, perhaps associated with local loss of cartilaginous rings. As we know, such defects can produce obstruction and atelectasis, which is what we are concerned with here.

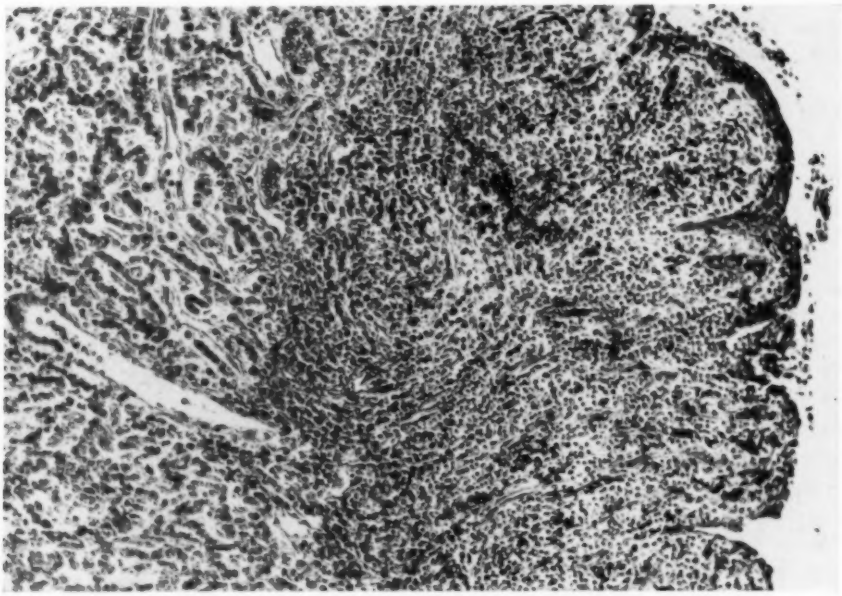

Fig. 3.—Photomicrograph. Tumor. At left are strands and columns of small round cells. At right are the eroded metaplastic epithelium and subepithelial inflammatory tissues. (Toluidine blue eosin ×140.)

DR. VAWTER.—The second patient, at the time of bronchoscopy, was found to have a normal respiratory tree down to the level of the left main stem bronchus, which was found to be filled with a thick purulent material which could hardly be aspirated. About 30 ml. per cubic centimeter of this material was removed, uncovering a nubbin of granulation-type tissue which was avulsed

with considerable bleeding. More purulent exudate was released distal to this point. The microscopic appearance of this nubbin is that of an intact epithelial surface surmounting a dense zone of chronic inflammation, and within the tissue mass proper there is gland-like structure with ramifying channels (Fig. 3). This is a characteristic picture of one type of bronchial adenoma.

About a week after the bronchoscopy, when his drainage had lessened and he appeared to have improved, a left lower lobectomy was performed. In the bronchus there was a mass of pink tissue protruding into the lumen, which had only been incompletely avulsed by the surgical approach. The lymph nodes were greatly enlarged in the resected specimen, but were found, on section, to contain no evidence of tumor. The line of excision appeared adequate and there was a very severe chronic pneumonitis and obliterative bronchitis distal to this lesion.

This young patient with bronchial adenoma is the fifth or sixth case which has appeared in the literature. The youngest was about 4 years of age at the time of diagnosis.[2] He had involvement of regional lymph nodes, but remained well for at least two years following his surgical therapy.

DR. FARBER.—Did you find any changes in the epithelium elsewhere in the respiratory tree?

DR. VAWTER.—The metaplasia which was apparent on the biopsy is confined to that area.

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Comments on Current Literature

MUSCULAR DYSTROPHY

AT the Jackson Memorial Laboratory, Bar Harbor, Maine, in 1953, interest and vigilance on the part of a student apprentice led to the discovery of muscular dystrophy in laboratory mice.[1] This condition, which occurred spontaneously as a genetic mutation in the Bar Harbor 129 strain, a highly inbred strain of mice, is a primary muscle disease similar in some respects to progressive muscular dystrophy in the human subject. The muscular regions involved, the nature of the lesions in these muscles, and the sparing of the central nervous system suggest its similarity to the human form of the disease. In the mice affected, growth and development are retarded; there is early evidence of muscle atrophy, characteristic skin lesions, and a shortened life span. Histologic changes in the muscle are considered remarkably similar to those encountered in dystrophic human muscle. A longitudinal section shows small multinucleated muscle fibers separated from one another by edematous interstitial tissue. The fibers are poorly developed, relatively few in number in a given area, and there is little evidence of muscular regeneration. On establishment of the strain and careful genetic study,[1] the disorder in mice appeared to be inherited as an autosomal recessive trait, in contrast to at least one form of human muscular dystrophy which is thought to be sex linked.

From about 1956, when mice of this strain became available for investigation in other laboratories, enzyme studies have been carried out in these mice, together with chemical and metabolic studies. Attempts have been made to characterize this myopathic condition in mice more fully and to compare it with other forms of muscle wasting and with the findings associated with clinical muscular dystrophy in man.

Within the past few months, two reports have appeared which deal with enzyme and metabolic studies in the Bar Harbor 129 strain of mice. One of these, published in the *Proceedings of the Society for Experimental Biology and Medicine* for October, 1958, is the third of a series of enzyme studies in muscular dystrophy carried out by Weinstock and his co-workers, this one of the series by Weinstock, Epstein, and Milhorat.[2] By investigating a number of enzyme systems in the muscles, these authors sought to compare this form of myopathy in mice with other forms of muscle wasting. Previous investigations by these authors had included studies of the type of muscle wasting which occurs in experimental animals following vitamin-E deficiency and following neurotomy. For the enzyme studies in dystrophic mice, the strain 129 (dystrophic animals and their normal litter mates) was obtained from the Jackson Memorial Laboratory and fed a standard commercial mouse pellet diet. All animals were allowed free access to food and water. The strain was maintained in the new environment for a considerable period of time before the enzyme studies were initiated. According to the original description of this dystrophic strain by Michelson and her associates,[1] signs were apparent in dystrophic mice by the third

week of life, and the complete life span covered a range of from 1 to 6 months. In the investigations by Weinstock and his associates,[2] the mice were allowed an arbitrary span of from 46 to 110 days, average 68 days, the weight averaging 14.1 grams. The control group for these investigations was composed of heterozygous litter mates of the dystrophic mice; these were studied when they reached an average age of 63 days and a weight of 21.4 grams. Dystrophic animals were consistently smaller in size and lighter in weight than the controls and showed varying degrees of ataxia, atrophy, and attendant paralysis.

In the conduct of enzyme studies, Weinstock and his co-workers recognize the need for "a proper reference base for enzyme activity,"[2] since changes in muscle composition are associated with most wasting conditions. Accordingly, the enzyme studies were accompanied by determinations of dry weight and of total protein and collagen-nitrogen content of the muscle. Results of enzyme assays were evaluated on the basis of wet weight, dry weight, protein-nitrogen content, and noncollagen protein nitrogen of the muscle. On the basis of their experience and that of others, the authors feel that "the most accurate index of functioning muscle mass upon which to base enzyme activity is non-collagen protein nitrogen content."[2] An apparent decrease in enzyme activity, unless so based "might be nonspecific and only a reflection of over-all breakdown of muscle."[2] With these possibilities in mind, the authors investigated changes in the muscle composition and the activity of four enzyme systems in dystrophic and control mice. Total nitrogen and protein nitrogen contents of dystrophic muscle were reduced as compared with controls, while the collagen nitrogen was increased. The percentage of dry weight was unchanged. Aldolase activity of dystrophic muscle was decreased on the basis of wet or dry weight but was not changed on the basis of protein or noncollagen protein nitrogen content of muscle. The succinoxidase activity was not affected significantly by this form of muscular dystrophy in mice. Cytochrome oxidase and cathepsin activities did not appear markedly increased in the muscles of dystrophic mice; liver tissue showed no detectable changes as a result of the dystrophy. According to these authors, the changes observed in the muscle protein content of mice showing dystrophy are similar to those associated with muscle wasting as it occurs following vitamin-E deficiency, with the type of atrophy resulting from neurotomy, and similar to the changes considered to be the chief pathologic alteration in muscular dystrophy in human subjects. Studies by these authors are in progress which concern enzyme systems in the muscles of patients with muscular dystrophy, particularly with reference to the catheptic enzymes whose in vivo rule is not clearly established as yet. These catheptic enzymes appear to be "involved in protein catabolism and may be the common mechanism in muscular wasting due to a number of different causes."[2]

Another publication of special interest in this connection appeared in *Metabolism* for November, 1958. This report by Perkoff and Tyler[3] concerns creatine metabolism in the Bar Harbor 129 strain of dystrophic mice. Anomalies of creatine metabolism are known to be present in human muscular dystrophy. In normal human subjects there is minimal creatinuria; patients with muscular dystrophy, however, show marked creatinuria with great reduction in urinary creatinine; these patients are unable to store a creatine load. Since the muscle disease of the 129 dystrophic strain of mice resembles the human disease both objectively and in the pathologic findings, the authors were interested in pursuing comparative studies of creatine metabolism. At the present time there is considerable interest also in the relationship between anomalies in pentose metabolism and progressive muscular dystrophy.[4] For this reason, the authors have made a study of the urinary excretion of pentose by these mice and have isolated myoglobin from

normal and dystrophic mice for electrophoretic study.

The control mice remained normal throughout the course of the study. The dystrophic mice from the Bar Harbor strain showed the typical characteristics: small size, flexed posture, weak and atrophic hind limbs, thinning of fur, skin excoriations, etc. Histologic examination of hind-limb muscles revealed the changes associated with this condition in mice as originally described by Michelson and her co-workers[1]: lymphocytic infiltration, necrosis of muscle fibers, hyalinization of fibers with reduction in fiber diameter, and general loss of the muscle architecture. Ordinary laboratory mice and control mice from the Bar Harbor strain show about the degree of creatinuria expected. Dystrophic mice showed marked reduction in urinary creatinine with a comparatively marked creatinuria. On the administration of a creatine load, however, the dystrophic mice were slower in excreting the additional creatine than the corresponding controls. Pentose excretion did not appear to be altered significantly in the dystrophic mice. Myoglobin concentration proved to be lower in the dystrophic mice than in the control mice. Electrophoretically, however, the myoglobin from both groups of animals was normal.

In a well-rounded discussion, Perkoff and Tyler[3] bring out the similarities and the differences between the "dystrophic process in mice and that observed in human subjects. The hereditary character of the disease in mice, the localization and histologic characteristics of the lesions, and the decrease in the concentration of myoglobin with normal electrophoretic mobility are all similar to human muscular dystrophy."[3] While the urinary excretion of creatinine and creatine are similar to that seen in the human condition, certain differences are apparent. Ordinary laboratory mice and controls of the 129 strain regularly show a high degree of creatinuria, making evaluation on a quantitative basis somewhat difficult in mice. The authors point out that this is in contrast to the situation obtaining in human muscular dystrophy. They consider the myoglobin findings in mice more comparable to the situation in human subjects: myoglobins of control and of dystrophic mice show the same electrophoretic mobility, as is the case in man. The authors offer alternative explanations: that there may be an abnormality in myoglobin synthesis or destruction of myoglobin to account for the low myoglobin level in the muscles of the diseased animals, or the observed decrease in myoglobin concentration may represent loss of the myoglobin from damaged muscle.

As a result of these investigations, Perkoff and Tyler are inclined to believe that the disease in mice and in human subjects is basically similar: "In spite of the fact that dystrophic mice and dystrophic humans show differences in creatine metabolism, the disease as it occurs in mice is more like human muscular dystrophy than any other observed in experimental animals. For this reason, study of the animal disorder may yet yield information of value in increasing the understanding of the human disease."[3]

RUSSELL J. BLATTNER

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Correspondence

Dear Editor:

The typical practice of pediatrics includes the responsibility of assisting parents to cope with the various kinds of behavior problems which often arise in normal children. Many factors in our cultural milieu seem to make the rearing of children quite fraught with anxiety to parents. Guidance for parents appears to be the order of the day and the demand for it by the parents themselves is steadily increasing. Often confused by their efforts to find answers in various kinds of literature, parents turn to the pediatrician. Consequently, whether he wishes it or not, the pediatrician has become a counselor and psychotherapist to parents of normal children with psychological problems.

With extensive knowledge of children, reasonably good acquaintance with the parents, and a common-sense approach to the problem, the pediatrician is capable of satisfying the need of parents for guidance to a large degree. However, with some behavior problems, the pediatrician is not able to directly provide the kind of treatment which he considers to be indicated. Referral to psychiatrists and psychologists may not be appropriate because of the relatively minor nature of the problem in many instances. The cost of psychiatric care might be prohibitive in some other cases.

A good nursery school with a trained staff can be of specific value to the pediatrician. With such a school, the pediatrician has at his disposal facilities and personnel which ordinarily he does not have. The groups of children at nursery school offer an ideal setting to help the unsocialized child. With a group from which to choose, the normal but problematical child will find a friend and begin to develop social qualities. In his efforts to make and keep friends even the young child discovers that he must "share." The child learns to wait for his turn in many activities which he enjoys and in which he wants to participate. Temper tantrums can be handled matter-of-factly and casually by trained teachers. The children themselves often discourage the tantrums by such verbalization as "baby." Interestingly enough, groups of children can be sympathetic when they sense a child is truly troubled.

Make-believe families originate every day and every family has its baby. Sometimes with the aid of a teacher and sometimes without, the children act out the role of the mother with the baby, the baby's need of the mother's attention, the role of the big brother, and so on. Jealousy of the baby in the family is just one problem which often can be effectively handled in a nursery school through the proper use of the children's pretend families.

The child's need for achievement can be met in the nursery school setting with activities which can be scarcely duplicated at home. The child who especially needs to have limits set on his behavior and who has an overly amount of difficulty in accepting his parent's authority usually learns to conform in nursery school much more readily. He wants to do as the others do. Little children are inclined to tell each other to follow the rules. Again the child wishes to be accepted by the group and thus is inclined to want to follow the rules with fewer reminders from the teacher than from mother. Nursery school also offers the child an opportunity to express such feelings as hostility and aggression through safe channels guided by the teacher. These are but a few of the sort of problems which can be effectively dealt with in a nursery school setting.

A qualified and adequately trained director of a nursery school is capable of following through with suggestions made by the pediatrician. Furthermore, a trained staff is able to provide the pediatrician with impartial opinions and information based on

many hours of observation of the child in a variety of situations. A mother has an opportunity to ventilate her feelings at length and to profit from what she learns of the effective methods used in dealing with her child at the school.

Reports can be made available to the pediatrician so that he is aware of the progress being made in the solution of the problem and the child's personality development.

The greatest difficulty for the pediatrician lies in finding a nursery school to which he can refer children and feel confident of the treatment the children will receive. Many nursery schools, if not most, are directed by individuals who have only a smattering of education or whose education is not specifically related to children. Such directors usually increase the child's problem. State laws relative to nursery schools do not adequately control the situation and poor nursery schools outnumber the good ones. However, it would be worth the pediatrician's time to make some investigations and determine whether there is a good nursery school with a trained staff accessible to his patients.

HELENA STIEL, PH.D.
Los Angeles, Calif.

News and Notes

The following pediatricians were certified in the Subspecialty of Pediatric Allergy by the **American Board of Pediatrics, Inc.** on February 8, 1959, in Chicago, Illinois.

Dr. Daniel Blitz, 1 Club Drive, Woodmere, N. Y.

Dr. John Gerard Flynn, 377 Essex St., Salem, Mass.

Dr. John S. Hyde, 715 Lake St., Oak Park, Ill.

Dr. Raymond W. Latham, 421 Plaza Parkway Bldg., 4620 J. C. Nichols Pkw., Kansas City 12, Mo.

Dr. Richard Lawrence London, 300 South Goodman St., Rochester 7, N. Y.

Dr. Lloyd Stanley Nelson, 616 Marquette Bank Bldg., Minneapolis 2, Minn.

Dr. Ronald Reuben, 9735 Wilshire Blvd., Beverly Hills, Calif.

Dr. Alexander Roth, 71st Street & Tomahawk Road, Prairie Village 15, Kan.

Dr. Edward Louis Strem, 565 So. Snelling Ave., St. Paul 16, Minn.

The Eighth Congress of the **Pan-Pacific Surgical Association** will meet in Honolulu, Hawaii, September 28 through October 5, 1960. All members of the profession are invited to attend the Congress at which nine surgical specialty sections are scheduled simultaneously. Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association. Suite 230, Alexander Young Building, Honolulu 13, Hawaii.

The **Intermountain Pediatric Society** announces its annual meeting which is scheduled for June 26, 27, and 28 at Sun Valley, Idaho. Dr. Robert Alway, Dr. M. E. Lahey, Dr. Ralph Platou, and Dr. Josef Warkany will speak at the meeting which is open to all physicians. Sessions are daily from 8 A.M. until noon, with round table groups from noon until 1:30 P.M. For further information, write to Intermountain Pediatric Society, 2000 South 9th East, Salt Lake City, Utah.

Applications for the residency from January 1, 1960, to December 31, 1960, in Pediatric Oncology at **Memorial Center for Cancer and Allied Diseases** in New York will be received up to May 1, 1959. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th St., New York 21, N. Y.

The **Harvard Medical School** will offer the following postgraduate courses in pediatrics this spring:

Pediatrics 5, to be held June 1 to 12, inclusive, 1959, daily from 9:15 A.M. to 4:30 P.M., at Massachusetts General Hospital, will provide a general review with emphasis on recent advances and therapy. The first seven days are devoted to pediatric medical, surgical, orthopedic, cardiac, allergic, dermatologic, psychiatric, eye, ear, and x-ray problems. During the last four days, students will concentrate on disorders of growth and development, common endocrine problems, and the metabolic aspects of infant feeding, parenteral fluid therapy, and management of nephritic and diabetic patients.

Pediatric Metabolism and Endocrinology, to be held June 9 to 12, inclusive, 1959, daily from 9:15 A.M. to 4:30 P.M., at Massachusetts General Hospital, is the same course as the last four days of Pediatrics 3, as described above, but may be taken separately.

Those interested should write: Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston, Mass.

The Department of Dermatology of the **Temple University Medical Center** announces an intensive postgraduate course in Pediatric Dermatology to be given from Monday, April 27, to Friday, May 1, 1959, at The Skin and Cancer Hospital of Philadelphia.

The course is designed for the pediatrician with emphasis on diagnosis and treatment of the common dermatoses. Sufficient basic information will be presented so that the relationship between physiology and pathology can be appreciated.

Information concerning this course can be obtained by writing to: Dr. Carroll F. Burgoon, Jr., Medical Director, The Skin and Cancer Hospital of Philadelphia, 804 Pine St., Philadelphia 7, Pa.

The third annual postgraduate course in Fractures and Other Trauma will be presented by the *Chicago Committee on Trauma* of the **American College of Surgeons** from Wednesday, April 15, through Saturday noon, April 18, 1959, at the John B. Murphy Memorial Auditorium, 50 East Erie Street, Chicago 11, Illinois.

All phases of trauma will be discussed by outstanding teachers from the five medical schools and chiefs of service of leading hospitals in the Chicago area as well as distinguished guest speakers from other parts of the country.

Registration fee for the course is $75. Residents, interns, and students will be admitted free if a note of identification from chief of service or dean is presented.

A series of short refresher courses will be given during May and June, 1959, by **The Children's Hospital of Philadelphia** and by the Graduate School of Medicine, University of Pennsylvania.

Pediatric Advances, on May 25 through 29, 1959, will be conducted by the staff of the Children's Hospital of Philadelphia. The curriculum will consist of clinics, demonstrations, and panel discussions in selected aspects of contemporary pediatrics in which important advances are being made. *Note:* Interested physicians are urged to apply early since total attendance is limited. Registration fee will be refunded if the registrant later finds it impossible to attend. The tuition is $115.00.

Practical Pediatric Hematology on June 1 through 5, 1959, will be conducted by Irving J. Wolman, M.D., Thomas R. Boggs, Jr., M.D., and other members of the Hematology Department of the Children's Hospital of Philadelphia. The tuition is $125.00. The program on June 4 and 5 will be devoted to problems of blood grouping, neonatal jaundice, kernicterus, and exchange transfusions. Physicians may register for these 2 days only if desired. Tuition will be $50.00. An illustrative collection of 25 abnormal blood and bone marrow slides has been prepared. These are available for purchase: $10.00 for registrants, $15.00 for nonregistrants.

Postgraduate Course in Practical Pediatrics is for physicians in Pennsylvania, New Jersey, and Delaware. This course will be conducted by the staff of the Children's Hospital of Philadelphia, Wednesday afternoons from 1:00 P.M. to 5:00 P.M., March 18 through June 4. The tuition is $100.00.

Inquiries should be addressed to Irving J. Wolman, M.D., Director of Post-Graduate Education, The Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.

Books

Autonomic Imbalance and the Hypothalamus, Implications for Physiology, Medicine, Psychology, and Neuropsychiatry. Ernest Gellhorn, Minneapolis, 1957, University of Minnesota Press, 300 pages. Price $8.50.

Those pediatricians who are sufficiently interested in mechanisms of emotional response in normal and in psychiatrically impaired individuals to do some careful reading on this subject will find this book a gold mine. It is a mature, well-mediated, scientifically sound expression of one of our better neurophysiologists. It may cause little stir itself but, by intellectual ricochet, will affect much of clinically immediate research.

Much of the information in this most recent of Dr. Gellhorn's comprehensive works on autonomic regulation is concerned with new material in animal and human experimentation. Carefully standardized test observations of autonomic response, such as blood pressure, heart rate, and respiration, are performed under various experimental situations in which the subject has been conditioned or "tuned" by autonomically effective medications. The animal observations are carefully compared with those in normal and institutionalized psychiatric adults. From this comprehensive background study, he draws broad principles of evaluation of autonomic function and of autonomic reflections of normal and abnormal psychic states.

Dr. Gellhorn has not explored the corresponding pediatric clinical syndromes, although his methods, such as consecutive determinations of blood pressure after administration of Mecholyl or adrenalin, are fully adaptable to young children.

This book is not easy reading, but it is a major work of the quality and intellectual reach which is needed to accomplish progress in this most subtle field of clinical neurophysiology.

James F. Bosma

Traitement du Diabète Infantile en Régime Libre. P. Royer and H. Lestradet, Paris, France, 1958, Editions Médicales Flammarion, 190 pages. Price 3,500 francs.

In this concise booklet of 190 pages (including 6 pages of bibliography), the authors have summarized their experience in the management of some 800 diabetic children during the past ten years in the Hôpital des Enfants Malades at Paris, under the regimen popularly designated "free diet" (régime libre). The monograph is remarkably well organized, with excellent discussion of the physiopathology of diabetes mellitus and essential principles that should guide treatment, with due consideration of psychologic as well as physical needs for health, growth, and development. Practicality is emphasized. Questions that in the past have involved much controversial argument among experts in this field are discussed with great clarity and precision. The authors accept the fact that the term "free diet" has led to confusion in the interpretation of acceptable dietary rules; they prefer a term such as "normal unweighed diet" to differentiate this regimen from stricter schemes of treatment with diets weighed or measured according to carefully calculated prescriptions. Most essential, the authors insist, is flexibility in the adaption of daily insulin dosage to changing needs of the body.

Salient features of the text are indicated by the following selections from the table of contents: (1) bases of diagnosis and treatment, including a concise review of physiopathology; (2) methods of treatment: restrictive diet; normal diet, measured or unmeasured; different insulins, their action and reasons for choice of one or another insulin in individual cases; (3) practical considerations: adaptations of daily habits in the "manner of living" with diabetes; methods for urinalysis most practical for the patients and for their parents; technique of insulin injection and equipment needed; (4) treatment of acute complications, insulin resistance, ketoacidosis and coma, chronic complications, infections, etc.; (5) medicosocial problems, vacation camps, centers for education; lay associations (Association française des diabétiques; Association pour l'aide aux jeunes diabétiques).

Dr. Lestradet was a principal organizer of a series of summer camps for diabetic children (under the aegis of the International Children's Center) which serve a valuable purpose for educating the children in their self-management and for the encouragement of a "normal life." The camps are valuable also for the training of young pediatricians, nurses, and social workers concerned with the handling of diabetic children.

George M. Guest

Editor's Column

THE PROTEIN ALLOWANCE CONTROVERSY

THE papers of Gordon and of Holt in this issue present a critical analysis of the issues and data involved in the current controversy over the protein allowance for infant feeding.

In essence the controversy is between those who advocate a "low" protein intake simulating human milk and those who advocate a "high" protein intake such as is furnished by the conventional formula of ⅔ parts milk, ⅓ part water, and added carbohydrate. The low protein allowance suggested would supply approximately 2 Gm. per kilogram per day with 8 to 10 per cent of the calories from protein, while the high protein would supply 3.5 Gm. per kilogram per day with 15 per cent of the calories from protein. Actually, pediatricians have been using these two types of feedings for a number of years, probably without too much thought as to the differences in their composition and almost certainly without noting any important differences in the growth and development patterns of the infants receiving the feedings.

Why, then, has the issue developed and why is it important? In answer to the first part of the query, it should be pointed out that the problem which has given rise to the controversy is by no means new. In fact it arose when it was shown by chemical analysis many years ago that there was no deficiency in the essential amino acids in casein as applied to human nutrition. Previous to this it had been accepted generally that the protein of cow's milk was inferior to that of human milk, hence, more of it was needed by the formula-fed infant. But, the question was raised, if it is true that the protein of cow's milk and of human milk are biologically equivalent, why should the protein requirement of the formula-fed infant be different from that of the infant receiving human milk? In spite of the numerous studies that have been carried out (reviewed by Gordon and by Holt), no data up to the present time have been considered convincing enough to provide an acceptable answer either in favor of or against the low or high protein advocates. It was this impasse that led the Food and Nutrition Board of the National Research Council for the first time in its history to omit a recommended protein allowance in its 1958 issue of *Recommended Dietary Allowances*. Naturally, this action has had the effect of stimulating wide interest in a problem that has been troublesome to many in the field of infant nutrition for at least a quarter of a century.

Among the many studies of the past designed to shed light on the relative biologic values of human vs. cow's milk protein, those of Jeans and Stearns at Iowa City have perhaps received the most attention. They concluded from their well-known metabolism-ward experiments that artificially fed infants receiving protein and calcium intakes adjusted so that nitrogen and calcium retentions were of the same order as infants fed human milk did not perform in a variety of areas as well as breast-fed infants receiving the same levels of protein and of calcium or as well as artificially fed infants receiving higher intakes of protein and calcium. Jeans declared that the requirements of formula-fed infants should probably not be based upon the requirements of breast-fed infants. Presumably, his opinion had much to do with the recommended protein allowance of 3.5 Gm. per kilogram per day for infants under 6 months of age carried by the *Recommended Dietary Allowances* in all its issues previous to 1958.

However, there were reasons why these studies by Jeans and Stearns (see Gordon) could not be accepted as having proved the biologic superiority of human milk protein over cow's milk protein. Jeans himself stated in his presidential address before the American Pediatric Society in 1950: "The basis for the conceded superiority of human milk seems still to be something of a nutritional mystery."

More recently Foman and May, also at Iowa City, have attacked the problem anew, but thus far their studies have not been completed sufficiently to permit the drawing of definitive conclusions. It may seem strange to most that so much difficulty should have been encountered over the years in reaching an unequivocal decision about the relative nutritional efficiency of human and cow's milk protein. There is abundant clinical evidence derived from years of observation that formula-fed infants receiving high protein allowances compare favorably to thriving breast-fed infants. Can the infant fed 2 Gm. of protein per kilogram per day match their performances? This would appear to be the question that must be answered before the controversy can be settled.

It is of interest that Gordon and Holt, both acknowledged authorities in the field of infant nutrition, reach much the same conclusion after their extensive and critical analysis of pertinent data. Both agree that there is insufficient evidence from the work done thus far upon which to base a firm judgment either for or against high or low protein feedings. Gordon, however, clearly states his preference for retaining the protein allowance of 3.5 Gm. per kilogram per day. Holt, on the other hand, while he frankly admits he does not know the answer to whether we are safer with 2 or 3 Gm. or more of protein per kilogram in infant feeding, gives one the impression he is not convinced the lower protein levels may not be enough.

If we turn now to the second part of our query (Why is the issue over a high vs. low protein allowance important?), several reasons may be advanced. First, it is important because it represents an unanswered challenge in the field of infant nutrition. A problem exists for which a solution has not been found. To the true scientist, regardless of all other considerations,

this is a state of affairs not to be tolerated. It seems safe to predict that the present controversy will serve as a spur to further and more exact investigations. When the incontrovertible evidence is finally at hand, the history of infant feeding will have recorded another important advance.

The problem is important also to the physicians of the nation who prescribe feedings for infants. True, infants exhibit a surprising degree of adjustability to wide variations in composition of feedings offered, and so long as intake is not limited they do quite well for themselves in response to their own built-in regulatory mechanisms. Nevertheless, the responsibility rests with the physician to be familiar with the composition of the feedings he prescribes. It may be that the present controversy will serve a most useful purpose by making physicians more aware of the complexities of infant feeding and the need for a more critical evaluation of what is prescribed in terms of its nutritional potential.

Another group to whom the protein allowance in infant feedings is important consists of the manufacturers of infant foods. Naturally, the manufacturers of the products simulating human milk would be pleased to have the low protein advocates proved correct, while the evaporated milk industry and the others whose products contain the high protein levels would be equally pleased to have the issue resolved in favor of their products. It is easy to speculate that the present controversy may have been stimulated by, even financed and supported by, industrialists seeking advantage for their particular products. While it is probably true that both the low and high protein advocates have their counterparts among the industrialists, nevertheless, we believe all are equally interested in establishing scientific truths and that when these have been established the manufacturers will not hesitate to adjust their products accordingly.

Finally, consideration must be given to the importance of a protein allowance for countries other than our own. Recently the Food and Agricultural Organization of WHO has recommended that "2 grams of protein per kilogram may be taken as a satisfactory figure for the requirement of the young infant up to six months when the protein is from breast milk or cow's milk supplied in a form readily digested by the infant." It is necessary here to know what purposes FAO had in mind in making such a recommendation. We would presume it was meant to apply to areas in which the milk supply was not as plentiful as in the United States, and that minimal allowances rather than optimal allowances were being defined.

In the current *Recommended Dietary Allowances* (publication 589), the following discussion of protein allowances occurs in the text. "The protein in human milk represents about 8 per cent of the total calories. Available evidence does not permit conclusions as to whether there is or is not a significant difference in the biologic value of the proteins in human milk and cow's milk. Levels of intake of 3.5 grams per kilogram from age 1 month to 6 months, and of 3.0 grams per kilogram during the remainder of the first year, are undoubtedly well in excess of minimum requirements and afford ample allowances to meet the needs of healthy infants. Allowances for the

artificially fed infant may lie in the range of 2.5 to 3.5 grams per kilogram from 2 to 6 months and 2.0 to 3.0 grams per kilogram during the remainder of the first year. In current practice, diets furnishing 3.5 grams of protein and more per kilogram are in common use."

This brief summation makes it clear why the Food and Nutrition Board deemed it advisable to leave blank the space reserved for a recommended protein allowance for infants. But until the controversy is settled by the accumulation of convincing evidence gained from adequate clinical trial and metabolic data, there would appear to be no good reason why physicians need modify a feeding practice which has demonstrated its general satisfactoriness over a period of many years. Studies have shown that healthy infants in good homes in this country ingest even larger amounts of protein, rather than less, than the recommended 3.5 Gm. per kilogram. To reduce the protein intake of formula-fed infants to the levels found in human milk in an area where higher levels are readily available would seem impractical.

Lee Forrest Hill

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IN this issue the question of optimal protein allowances for infants is discussed in detail by Gordon and Holt.

Gordon presents a systematic analysis of the evidence supporting the efficacy of protein intakes lower than 3 to 4 Gm. per kilogram per day (15 per cent of the suggested calories). The evidence accumulated from nitrogen balance studies, growth curves, and many biochemical investigations does not substantiate unequivocally the validity of 2 or 3 to 4 Gm. per kilogram protein allowances.

Such a finding is not unexpected. Inherent in studies of the effects of intake on body composition are certain systematic errors. First, retention in balance studies represents the small difference between two very large quantities—intake and output. Almost invariably, a high intake mathematically leads to greater retention since unavoidable small errors in balance technique—regurgitation, stool and urine losses—lead to artifactual retentions. If absolute intake is greater, the same percentage errors in analyses and procedure lead to greater calculated retention.

Second, since most studies are carried out with intake related to body weight or a factor thereof, acute retention of water with one or another feeding regimen automatically guarantees a greater food intake (calories, protein, etc.) per unit of active cell mass. Therefore, feeding mixtures with greater solute retention (particularly NaCl) cannot be equated with those of lower solute retention on a per kilogram basis. Since surface area is derived from weight, the same difficulty obtains to a degree. This principle has been largely ignored in feeding studies, but small differences in intake per unit of active mass become large when projected over long periods.

I believe it is appropriate that no rigid allowance is set down in the *Recommended Dietary Allowances* of the Food and Nutrition Board. Optimal feeding must be considered in terms of that feeding mixture which provides the largest margin of safety under the environmental conditions existing and in the particular infant.

Since environment such as temperature is not static and since the infant is in a constant state of physiologic maturation, optimal allowance for protein in relation to calories and water cannot be stated for all infants everywhere.

Regardless of the final opinion of these authors, an important contribution that these papers make to the practitioner is to remind him that the feeding of infants is still an important aspect of pediatrics which demands his awareness of advances in physiology and nutrition.

Robert E. Cooke

FOREIGN LECTURESHIP PROGRAM FOR 1959

AS ANNOUNCED in the JOURNAL of last November, a change has been made in the Journal of Pediatrics Educational Foundation "Foreign Lectureship" program for 1959 due to the triannual meeting of the International Congress of Pediatrics in Montreal the week of July 19, 1959. Eight lecturers, selected by the Foundation from a list of names suggested by the program committee of the Congress, were invited and have accepted the invitation of the Foundation to spend the week of July 12 as a visiting lecturer. Through the cooperation of departmental chiefs of staff, the requests of some of the lecturers to spend the week at a particular clinic for one reason or another have been met. The list is as follows:

S. T. Achar, Madras, India, Professor of Pediatrics at the University of Madras and Director of the Institute of Child Health in Madras.

E. K. Ahvenainen, Jyväskla, Finland, a pathologist who has made many contributions to pediatric pathology.

Horst Bickel, Marburg, Germany, Professor of Pediatrics at the University of Marburg.

K. C. Chaudhuri, Calcutta, India, Director of the Institute of Child Health in Calcutta, and Editor of the Indian Journal of Pediatrics.

Wilfred Gaisford, Manchester, England, Professor of Child Health at the University of Manchester.

E. Kerpel-Fronius, Pecs, Hungary, Professor of Pediatrics at the University of Pecs.

J. P. M. Tizard, London, England, member of the staff of the Institute of Child Health in London.

Rolf Zetterström, Göteborg, Sweden, Professor of Pediatrics at the University of Göteborg.

Dr. Bickel will spend the week at the Children's Research Foundation, Cincinnati; Dr. Ahvenainen at the Babies Hospital in New York; Dr. Zetterström at the Children's Memorial Hospital, Chicago; Dr. Tizard at the Department of Pediatrics of the

Western Reserve Medical School, Cleveland; Dr. Gaisford at the Children's Hospital in St. Louis; Dr. Chaudhuri at New York University–Bellevue Medical Center, New York; and either Dr. Achar or Dr. Kerpel-Fronius at the Hospital for Sick Children, Toronto, and the other at a clinic in the United States.

The Foundation plans to return in 1960 to a foreign lectureship program similar to that of last year, when Dr. Hallman was visiting lecturer for a week at a number of clinics at a more favorable time of the year.

The list of domestic lecturers for 1959 is not complete at the time this issue of the JOURNAL goes to press.

Erratum

In the article entitled "Cardiovascular Surgery in a Children's Hospital. II. Cyanotic Lesions," by Dr. Rachel Ash, Dr. Julian Johnson, Dr. C. Everett Koop, Dr. Sidney Friedman, and Dr. William Rashkind, which appeared in the March issue of the JOURNAL, in Table I, the number of deaths among children with transposed great vessels should be 13, not 10, the percentage of deaths, 76.4. The total number of deaths should be 48, and the total percentage of deaths, 11.0.